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Original Communications

THE RELATIONSHIP OF THE ESTROGENS AND PROGESTERONE TO THE EDEMA OF NORMAL AND TOXEMIC PREGNANCY*

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THE tendency to retain water in the tissues is a well-recognized characteristic of normal pregnancy. In the specific toxemias, a further decrease in the ability to eliminate water results as a rule in greater degrees of edema. Following both normal and toxemic pregnancy, the excess water is rapidly eliminated during the first few days of the puerperium.

In a previous report, we submitted evidence to show that the retention of sodium and water during pregnancy was due to the estrogenic material produced by the placenta and its loss during the puerperium to the disappearance of the estrogens. In the present study, the relationship has been further investigated by the administration of large doses of these substances during pregnancy and the puerperium.

Introduction

The retention of water in normal pregnancy is indicated by the degree of weight gain, by the frequent slight edema of the lower extremities, by an increase in the volume of plasma[1, 17, 31] and of extracellular water.[8] The rise in plasma volume is manifested by an increased water

*This study was carried out with the aid of a grant from the Commonwealth Fund.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

content of the blood,[19, 36] a reduction of red cell count, hemoglogin, hematocrit[13, 15] and plasma proteins.[39, 40] This increase is said to reach a maximum of 25 per cent or more at the ninth lunar month after which some diminution occurs before labor.[17, 50] The usual proportion of available extracellular water in pregnant women weighing less than 120 pounds has been found to range from 33 to 37 per cent of the total body weight, as compared to an average of twenty to 26 per cent in nonpregnant women.[8]

The retention of sodium parallels that of water, for a consistently positive balance, for this ion has been shown to exist during the latter months of pregnancy.[11, 21, 48, 49] A part of the positive sodium balance can be attributed to the needs of the developing maternal and fetal tissues, but there is in addition an altered capacity of the pregnant woman to eliminate sodium. This is shown in the retention of relatively large proportions of administered sodium chloride,[34, 41] and in the delayed elimination of measured quantities of ingested water.[30, 35]

With parturition changes in these relationships set in. During labor and immediately afterwards, the blood becomes more concentrated.[1, 17] This is in part due to blood loss, partly to the effects of muscular effort and dehydration and perhaps in part to a redistribution of water as a result of the disappearance of the placental circulation. This period of blood concentration is of short duration, however, for within forty-eight hours the plasma volume again rises[1, 13, 39] and immediately thereafter diuresis commences. Large quantities of sodium appear in the urine during the next few days[48] and there is a considerable loss of available extracellular water.[8] The secondary expansion in the plasma volume after delivery may be attributed to the return of the excessive quantities of interstitial fluid to the vascular stream. This in turn leads to the diuresis of the early puerperium.

In the specific toxemias of pregnancy, pre-eclampsia and eclampsia, somewhat different conditions obtain. Here the edema, gain in weight and water retention are greater. The capacity rapidly to eliminate excessive sodium is apparently further reduced and administration of sodium chloride may precipitate a considerable exacerbation of symptoms.[26, 27, 46] Water diuresis is also further delayed.[35] The blood in pre-eclampsia does not partake in the fluid increase, however, for now, as numerous observers have pointed out, there is a relative concentration of the blood as indicated by increase in cell volume, hemoglobin, proteins, and certain other constituents of the blood.[13, 42, 44] Albers[1] has recently reported a greatly reduced plasma volume in "hydrops gravidarum." Blood dilution occurs with clinical improvement during the course of the toxemia and follows rapidly the death of the fetus or parturition.[42] The fact that in toxemia there is increased water in the tissues and a relative hemoconcentration suggests that the water retention is due to a barrier between tissue and blood stream and not between blood stream and kidney.

In a previous paper by us,[48] the retention of sodium and water in pregnancy was attributed to the high estrogen and progesterone content of the body fluids. The evidence for this theory was found partly in reports from the literature indicating the sodium and water retaining properties of the estrogens and progesterone, partly from our own correlation of urinary estrogen and pregnanediol with sodium balance before and after labor.

a. The water and sodium retaining effects of the estrogens, and to some extent of progesterone, are evident from several types of observation. A retention of salt and water during the phase of sexual skin swelling of monkeys has been noted repeatedly;[20, 32] retention of sodium and water also precedes menstruation in women.[52] The injection of estrogens results in the retention of sodium and water in dogs[51] and in monkeys.[25] Progesterone in large doses, 15 to 20 mg., has a similar effect in dogs.[51]

That a large proportion of the unexcreted water may be found in the organs of reproduction is true,[2, 3, 47] but other organs partake in a general redistribution.[56] Clarke[9, 10] noted an increase in extracellular fluid and in a few observations slight hemoconcentration at the time of sexual skin swelling in the baboon. This is in some contrast to observations made several years ago of pronounced increase in blood volume in women and animals after the injection of relatively small quantities of estrogenic substance.[22-24] Selye and Bassett's[43] observation of a diuretic action of progesterone is also difficult to reconcile with other observations. Perhaps particularly relevant is a recent communication of Cantarow and Rakoff[6] who found that progesterone, as well as desoxycorticosterone, increased the rate of diffusion of sodium and chloride into the peritoneum. These observations, in the opinion of the writers, supported the view that such agents have an effect upon membranes in general and that the decreased excretion of sodium and chloride produced by them might be simply secondary to extrarenal phenomena.

b. In our previous publication,[48] complete sodium balances were determined on 6 pregnant women for at least ten days before and ten days after delivery. It was noted that in all estrogen and pregnanediol excretion ceased shortly before the previously positive sodium balance became negative and the post-partum diuresis commenced. In one case intrauterine fetal death before the onset of labor was preceded by a sharp decrease in estrogens and pregnanediol in the urine and by a negative sodium balance beginning nearly four weeks ante partum. In a final case it appeared that the administration of estrogens in the puerperium reduced the loss of sodium. It was concluded that certain of the placental hormones, notably the estrogens, were factors in the retention of sodium during pregnancy.

The present communication reports the results of the administration of estrogens and progesterone on the excretion of sodium during pregnancy and in the puerperium. This work was undertaken for two purposes.

a. Hormones During the Puerperium.—The increased excretion of sodium and water during the puerperium is quite evidently a reflection

TABLE I. EFFECT OF ESTRADIOL BENZOATE ON SODIUM BALANCE IN NORMAL PREGNANCY AND PUERPERIUM (CASE 6)

CLINICAL					SODIUM BALANCE						
DAYS	BLOOD PRESSURE	WEIGHT IN POUNDS	PROTEINURIA IN GM./LITER	URINE VOLUME IN C.C./DAY	DIET AS ANALYZED GM.	URINE GM.	FECES GM.	LOCHIA AND BLOOD LOSS AT DELIVERY	BLOOD FOR STUDY	DAILY BALANCE	TREATMENT
23		126½	0	990		0.58	0.015		0.04		
22		125	0	2.180	2.45	2.81	0.015			−0.38	
21		124	0	1,270	2.45	0.73	0.015			+1.70	
20		124	0	1,655	2.45	1.62	0.063			+0.77	
19	100/70	123½	0	1,635	2.30	1.04	0.063			+1.20	
18	106/68	124½	0	1,530	2.30	1.39	0.063		0.06	+0.79	
17	108/70	124	0	2,160	2.30	1.51	0.063			+0.73	
16	106/70	124	0	1,175	2.32	0.91	0.063		0.08	+1.27	30,000 R. U.
15	102/68	124¼	0	1,680	2.32	1.71	0.063		0.06	+0.49	90,000 R. U.
14		124	0	2,245	2.32	2.11	0.020			+0.19	60,000 R. U.
13	102/78	125	0	1,205	1.86	2.20	0.020			−0.36	
12	92/64	125¼	0	1,425	1.86	1.01	0.020			+0.83	
11	96/60	125¾	0	1,660	1.86	0.63	0.020		0.06	+1.15	
10	92/60	126	0	1,335	1.74	0.60	0.013			+1.13	
9	100/68	126	0	1,410	1.74	0.85	0.013			+0.88	
8	100/64	125½	0	1,770	*1.45	1.23	0.013			+0.21	
7	92/60	124	0	1,270	2.39	0.99	0.013		0.06	+1.33	
6	92/56	125	0	1,230	2.39	1.26	0.013		0.01	+1.11	
5	105/70	125	0	1,250	2.39	1.07	0.107			+1.21	
4	95/72	125	0	1,070	2.34	0.27	0.107			+1.96	
3	94/78	125½	0	1,660	2.34	2.18	0.107			+0.05	
2	106/78	125¾	0	1,420	2.34	0.63	0.107		0.07	+1.53	
1	110/86	125½	0	1,325	1.88	0.53	0.107			+1.24	

Day of labor											
	110/86	125	0	964	*1.95	2.08	0.367	1.364	0.14	−2.00	
1	85/50		Trace	1,575	2.38	0.41	0.028	0.254	0.06	+1.63	60,000 R. U.
2	92/58		Trace	1,545	2.76	0.87	0.028	0.254	0.06	+1.55	60,000 R. U.
3			0	1,350	2.76	1.36	0.028	0.127	0.05	+1.20	60,000 R. U.
4			0	1,680	2.76	4.60	0.028	0.127	0.07	−2.07	60,000 R. U.
5			0	1,870	2.12	0.96	0.028	0.127	0.06	+0.95	60,000 R. U.
6			0	1,480	2.12	1.08	0.026	0.206	0.01	+0.80	
7		114	0	1,435	2.12	1.95	0.026	0.203	0.01	−0.07	
8		113	0	1,890	2.22	2.30	0.026	0.206	0.08	−0.39	
9		114	0	1,850	2.22	2.13	0.026	0.140	0.01	−0.09	
10		113	0	1,705	2.08	0.57	0.026	0.140	0.06	+1.28	
11		112	0	1,295	2.44	0.37		0.140	0.01	+1.92	
12		113	Trace	1,550	2.44	0.21		0.045	0.01	+2.18	
13		114	0	1,700	2.44	2.34		0.045	0.07	−0.02	
14		114	0	1,400	2.44	1.09		0.045	0.01	+1.30	

*On this day part of food was refused or vomited. The figure for sodium intake was obtained by analyzing vomitus or rejected food and subtracting this from the sodium of the twenty-four-hour diet.

TABLE II. EFFECT OF ESTRADIOL BENZOATE ON SODIUM BALANCE IN TOXEMIA OF PREGNANCY (CASE 7)

CLINICAL					SODIUM BALANCE						
DAYS	BLOOD PRESSURE	WEIGHT IN POUNDS	PROTEIN-URIA IN GM./LITER	URINE VOLUME IN C.C./DAY	DIET AS ANALYZED GM.	URINE GM.	FECES GM.	LOCHIA AND BLOOD LOSS AT DELIVERY	BLOOD FOR STUDY	DAILY BALANCE	TREATMENT
23		154	4.0	1,580	2.06	2.32	0.030		0.066	−0.36	
22		153½	3.6	1,270	2.06	1.78	0.030			+0.25	
21		153½	3.8	1,610	2.06	2.15	0.030			−0.12	
20		152	3.2	1,180	2.06	1.58	0.030			+0.45	
19		153	4.0	1,450	2.06	2.54	0.030			−0.51	
18		151½	4.0	1,085	2.06	1.51	0.030			+0.52	
17	162/118	152¼	3.0	1,420	2.02	2.00	0.015			0.00	
16	176/128	153	3.4	1,040	2.02	1.68	0.015		0.066	+0.26	
15	160/115	152	3.8	1,940	2.02	2.33	0.015			−0.33	
14	160/120	152¼	4.2	2,105	2.02	2.47	0.015			−0.47	60,000 R. U.
13	152/115										
	164/108	152	4.8	1,880	2.02	2.24	0.015			−0.24	60,000 R. U.
12	150/104	152	4.4	1,210	2.02	1.45	0.015		0.075	+0.48	60,000 R. U.
11	148/100	153	3.0	1,740	*1.74	1.67	0.129			−0.06	
10	146/108	153	3.6	2,095	2.02	2.45	0.129			−0.56	
9	148/104	152	3.6	1,865	2.02	1.77	0.129		0.058	+0.06	
8	136/104	152	3.2	1,170	*1.08	0.88	0.129			+0.07	
7	168/124	150	4.2	890	2.02	0.63	0.040			+1.35	
6	176/126	151	5.2	890	2.02	0.53	0.040			+1.45	
5	168/128										
	150/112	152	5.0	950	2.02	1.03	0.40			+0.95	
4	152/108	152¼	4.2	1,750	2.02	1.10	0.040			+0.88	
3	160/124	153	5.4	1,050	2.35	0.93	0.078			+1.34	
2	150/110	154	5.0	1,230	2.35	0.68	0.078		0.103	+1.49	
1	144/110										
	138/102	155	4.4	1,280	2.35	0.63	0.078			+1.64	

Day of labor											
	154/110										
	146/100		2.6	1,026	*0.64	0.67	0.334	†0.330		–0.69	30,000 R. U.
1	150/108										
	154/110		1.6	1,865	*1.43	2.63	0.256	0.105	0.052	–1.61	30,000 R. U.
2	160/110										
	154/100		2.0	1,600	*1.26	3.84	0.256	0.105		–2.94	30,000 R. U.
3	140/98										
	140/88		1.4	2,060	2.35	4.50	0.120	0.091		–2.36	30,000 R. U.
4	144/94										
	138/88		1.2	1,780	2.52	3.92	0.120	0.091	0.052	–1.65	30,000 R. U.
5			1.6	1,617	2.52	3.15	0.119	0.091		–0.84	30,000 R. U.
6			1.7	1,680	2.52	2.62	0.119	0.034		–0.25	
7			1.2	1,945	2.52	1.68	0.119	0.034		+0.69	
8			1.2	2,110	2.52	2.14	0.042	0.034		+0.30	
9		133	1.8	1,395	2.52	1.58	0.042	0.033		+0.86	
10	130/80	133	1.8	1,420	2.52	1.27	0.042	0.033		+1.17	
11	132/104	132½	1.4	1,480	2.55	2.82	0.042	0.033		–0.35	
12		132½	1.0	1,990	2.55	1.40	0.042	0.033	0.052	+1.02	
13	140/80	132	Trace	3,407	2.55	4.70	0.042	0.033	0.215	–2.44	

*See footnote, Table I.

†This figure represents net sodium loss from post-partum hemorrhage partly balanced by transfusion.

TABLE III. EFFECT OF ESTRADIOL ON SODIUM BALANCE IN A NORMAL PREGNANCY AND PUERPERIUM (CASE 8)

CLINICAL					SODIUM BALANCE						
DAYS	BLOOD PRESSURE	WEIGHT IN POUNDS	PROTEIN-URIA IN GM./LITER	URINE VOLUME IN C.C./DAY	DIET AS ANALYZED GM.	URINE GM.	FECES GM.	LOCHIA AND BLOOD LOSS AT DELIVERY	BLOOD FOR STUDY	DAILY BALANCE	TREATMENT
10		134	0	1,725	2.53	1.14	0.005		0.113	+1.27	
9		134	0	2,120	2.53	1.95	0.005			+0.58	
8		134	0	1,615	2.53	1.68	0.005			+0.85	
7		135	0	1,875	2.53	2.10	0.005			+0.43	
6		135	0	2,185	2.53	3.51	0.005			−0.99	
5		134	0	1,615	2.51	1.63	0.012			+0.87	
4		134½	0	1,900	2.51	1.62	0.012			+0.88	
3		135	0	2,425	2.51	1.81	0.012		0.113	+0.58	
2		135	0	2,325	2.51	2.64	0.012			−0.14	10 mg. estradiol
1		135	0	2,100	2.51	1.91	0.037		0.091	+0.47	10 mg. estradiol
Day of labor			0	2,640	*2.39	1.60	0.037	0.213	0.837	−0.30	5 mg. estradiol
1			0	2,155	2.51	1.28	0.009	0.279	0.100	+0.84	5 mg. estradiol
2			Trace	2,115	2.04	2.12	0.009	0.249		−0.34	5 mg. estradiol
3			Trace	2,465	2.04	2.18	0.009	0.127		−0.28	5 mg. estradiol
4			Trace	2,170	2.04	2.72	0.009	0.127	0.102	−0.92	5 mg. estradiol
5			Trace	1,760	2.04	2.59	0.009	0.090		−0.65	
6			Trace	1,815	2.04	1.71	0.009	0.060		+0.26	
7			Trace	2,195	2.04	1.81	0.005	0.060		+0.17	
8			Trace	2,295	2.04	2.46	0.005	0.040		−0.47	
9			0	1,970	2.09	1.30	0.011	0.040		+0.74	
10			0	2,600	2.09	2.94	0.011	0.040		−0.90	
11			Trace	1,960	2.09	2.23	0.011	0.040		−0.19	
12		124	Trace	1,500	2.09	1.12	0.011	0.008		+0.95	
13	130/80	124½	Trace	2,775	2.09	2.32	0.011	0.008		−0.25	

*See footnote, Table I.

TABLE IV. EFFECT OF PROGESTERONE ON SODIUM BALANCE IN A NORMAL PREGNANCY AND PUERPERIUM (CASE 9)

CLINICAL					SODIUM BALANCE						
DAYS	BLOOD PRESSURE	WEIGHT IN POUNDS	PROTEINURIA IN GM./LITER	URINE VOLUME IN C.C./DAY	DIET AS ANALYZED GM.	URINE GM.	FECES GM.	LOCHIA AND BLOOD LOSS AT DELIVERY	BLOOD FOR STUDY	DAILY BALANCE	TREATMENT
11	110/80	128½	0	2,110	2.59	1.71	0.018		0.071	+0.79	
10	100/80	129	0	2,000	2.59	1.74	0.018			+0.83	
9	114/76	129	0	1,960	2.59	1.82	0.018			+0.75	
8		130	0	2,390	2.31	2.11	0.018			+0.18	
7		130	0	2,250	2.85	1.64	0.007			+1.20	
6	112/80	130	0	2,340	2.85	1.94	0.007			+0.90	
5		129½	0	2,460	2.85	2.35	0.007		0.078	+0.42	
4	115/91	129½	0	2,200	2.85	2.26	0.007			+0.58	
3	109/91	129½	0	2,410	2.85	1.85	0.014			+0.99	
2	114/94	129½	0	2,185	2.85	2.68	0.014		0.090	+0.07	
1		129½	0	2,500	2.47	2.81	0.014			−0.35	
Day of labor	110/90		0	1,520	2.47	1.73	0.014	0.780	0.070	−0.12	25 mg. progesterone
1	120/85		0	2,300	2.47	4.55	0.070	0.086		−2.24	25 mg. progesterone
2			Trace	2,405	2.47	2.54	0.070	0.086	0.078	−0.30	25 mg. progesterone
3			Trace	2,960	2.47	3.54	0.070	0.240		−1.38	25 mg. progesterone
4			Trace	2,660	2.47	1.99	0.070	0.052		+0.36	25 mg. progesterone
5			Trace	3,030	2.58	2.89	0.070	0.052		−0.43	
6			Trace	2,675	2.58	2.77	0.070	0.051		−0.31	
7			Trace	2,385	2.58	1.68	0.070	0.051		+0.78	
8			Trace	2,165	2.58	2.09	0.070	0.048		+0.37	
9			Trace	1,790	2.58	1.80	0.067	0.048		+0.67	
10			Trace	2,335	2.58	2.20	0.067	0.050		+0.26	
11		119½	Trace	2,200	2.45	1.03	0.067	0.050		+1.30	
12		119½	Trace	2,350	2.45	1.26	0.067	0.024		+1.10	
13		119½	Trace	2,000	2.45	1.50	0.031	0.024		+0.90	
14		120	Trace	2,270	2.45	1.80	0.031	0.024		+0.60	
15		119½	Trace	2,420	2.45	2.49	0.031	0.024		−0.10	
16		120	Trace	2,190	2.45	1.98	0.031	0.022		+0.42	
17		120	Trace	2,125	2.45	2.06	0.040	0.022		+0.33	
18		120	Trace	2,265	2.45	2.19	0.040	0.022		+0.20	
19		120	Trace	2,510	2.45	1.63	0.057	0.022		+0.74	
20	115/90	120	Trace	2,490	2.45	1.37	0.057	0.022		+1.00	

TABLE V. EFFECT OF PROGESTERONE ON SODIUM BALANCE IN TOXEMIA OF PREGNANCY (CASE 10)

CLINICAL					SODIUM BALANCE						
DAYS	BLOOD PRESSURE	WEIGHT IN POUNDS	PROTEIN-URIA IN GM./LITER	URINE VOLUME IN C.C./DAY	DIET AS ANALYZED GM.	URINE GM.	FECES GM.	LOCHIA AND BLOOD LOSS AT DELIVERY	BLOOD FOR STUDY	DAILY BALANCE	TREATMENT
53	110/76 124/100	163½	1.5	1,300	2.23	1.51	0.018			+0.70	
52	125/86 124/102	163½	1.5	1,240	2.23	1.27	0.018			+0.94	
51	121/85 124/100		2.0	915	2.23	1.38	0.018			+0.83	
50	108/80 118/92	165	1.5	1,390	2.23	1.04	0.098			+1.09	
49	108/84 130/98	165	1.4	638	2.23	1.27	0.098			+0.86	
48	125/95 130/105	165	1.5	875	2.23	1.40	0.098			+0.73	
47	115/80 110/86	165	1.0	690	2.47	1.45	0.098			+0.92	
46	110/84		1.2	840	2.47	1.47	0.032		0.065	+0.90	
45	120/94	163½	1.4	798	2.47	1.78	0.032			+0.66	25 mg. progesterone
44	120/80	163½	1.2	830	2.47	1.34	0.032			+1.10	25 mg. progesterone
43	116/88 120/100	163½	1.2	740	2.47	1.27	0.032			+1.17	
42	116/184 110/80	163½	1.5	1,050	2.47	1.48	0.032		0.080	+0.88	
41	126/86 128/86	165	1.4	1,340	2.25	1.94	0.023			+0.29	
40	120/80 126/96	164½	1.4	1,090	2.25	1.86	0.023			+0.37	
39	118/88	165	1.5	675	2.25	1.82	0.023			+0.41	
38	128/84	165½	1.4	600	2.25	1.87	0.023			+0.36	
37	135/90	166	1.6	670	2.25	1.97	0.027			+0.25	

36	106/86	165½	1.6	690	2.25	2.00	0.027			+0.22	
35	128/92	165	1.8	545	2.08	1.37	0.027			+0.68	
34	134/92	166	1.5	1,140	2.08	2.71	0.041			−0.67	
33	106/90	166½	2.0	1,120	2.08	1.80	0.041			+0.24	
32	118/90		2.0	975	2.08	1.92	0.041			+0.12	
31	116/88	168	2.5	840	2.08	1.76	0.041			+0.28	
30	118/98		2.5	895	2.08	1.84	0.041		0.067	+0.13	
29	125/104		2.0	1,495	2.16	1.62	0.041			+0.50	100 mg. progesterone
28	128/94	167½	1.6	1,410	2.16	1.83	0.093			+0.24	100 mg. progesterone
27	122/92	167	1.9	1,198	2.16	2.21	0.093			−0.14	
26	136/98	167	2.4	570	2.16	2.00	0.093			+0.07	
25	138/108	167	2.4	590	*2.03	1.49	0.093			+0.45	
24	128/104	167	2.4	680	2.16	1.76	0.093		0.116	+0.19	
23	95/75	166½	2.6	690	2.16	1.12	0.049			+0.99	
22	128/102	166½	2.4	870	1.63	1.93	0.049			−0.35	100 mg. progesterone
21	134/100	167½	2.4	540	1.63	1.40	0.049			+0.18	100 mg. progesterone
20	128/84		2.2	780	1.63	2.03	0.049			−0.45	
19	116/96	166		330	1.63	0.95	0.101			+0.58	
18	128/108	165	2.2	670	*1.43	2.05	0.101			−0.72	
17			2.4	710	1.63	2.11	0.101			−0.58	
16	120/92	166	3.6	330	2.62	0.88	0.101			+1.64	
15	114/90	166	3.4	730	2.62	2.19	0.101			+0.33	
14	125/102	166	2.6	1,370	2.62	1.78	0.101			+0.74	
13	120/94	166	2.6	980	2.62	1.21	0.101			+1.31	
12	120/92	167	2.8	1,003	2.62	1.51	0.101			+1.01	
11	124/94	168	3.8	690	2.62	1.60	0.101			+0.92	
10	130/98	168	3.6	850	2.17	2.05	0.101		0.116	−0.10	
9	110/84	169	2.8	810	2.17	2.18	0.101			−0.11	
8	118/98	168	2.8	1,060	2.17	2.50	0.109			−0.44	
7	120/96	168	2.6	1,200	2.17	1.78	0.109			+0.28	
6	115/96	166½	3.6	820	2.17	2.50	0.109			−0.44	
5	100/90	166½	3.1	1,015	2.38	2.40	0.109			−0.13	
4	100/90	167	3.2	950	2.38	1.86	0.109			+0.41	
3		167	4.4	885	2.38	1.92	0.109			+0.35	
2	134/110	168	4.5	1,530	2.38	1.32	0.146			+0.91	
1	124/106	168	4.8	1,003	2.38	2.32	0.146		0.058	−0.14	

TABLE V.—CONT'D

CLINICAL					SODIUM BALANCE						TREATMENT
DAYS	BLOOD PRESSURE	WEIGHT IN POUNDS	PROTEINURIA IN GM./LITER	URINE VOLUME IN C.C./DAY	DIET AS ANALYZED GM.	URINE GM.	FECES GM.	LOCHIA AND BLOOD LOSS AT DELIVERY	BLOOD FOR STUDY	DAILY BALANCE	
Day of labor	140/120		4.2	470	*1.40	0.87	0.167	1.182		−0.82	50 mg. progesterone
	160/132										
1	130/90		1.8	1,250	2.17	3.60	0.021	0.377		−1.83	50 mg. progesterone
2	126/96		0.5	2,790	2.17	4.73	0.021	0.181		−2.76	50 mg. progesterone
3	126/100		2.0	1,345	2.17	3.06	0.021	0.253		−1.16	50 mg. progesterone
4	118/96		4.0	1,025	1.93	1.63	0.021	0.052	0.065	+0.16	50 mg. progesterone
5	120/100		4.0	840	1.93	0.99	0.021	0.052		+0.87	
6	96/80		3.0	865	1.93	0.88	0.021	0.050		+0.98	
7	116/96		2.8	815	1.93	0.85	0.021	0.050		+1.01	
8	116/94		2.2	1,245	1.93	2.14	0.021	0.048		−0.28	
9	112/94		2.6	1,740	1.93	2.27	0.021	0.048		−0.41	
10		154	2.0	1,065	1.93	1.39	0.021	0.048		+0.47	
11		154½	1.8	730	2.19	1.23	0.131	0.023		+0.81	
12		154	2.0	1,400	2.19	1.57	0.131	0.023		+0.47	
13		154	1.8	1,015	2.19	1.57	0.131	0.042		+0.45	
14		155½	2.0	710	2.19	1.06	0.131	0.042		+0.96	
15		153½	0.5	1,085	2.19	2.10	0.131	0.042		−0.08	
16	115/88	153	0.2	690	2.19	1.15	0.131	0.042		+0.87	

*See footnote, Table I.

of some physiologic change caused by the loss of the fetus or the placenta. Although the final elimination of the estrogens and progesterone, with their known sodium retaining properties, seems a satisfactory explanation, other possible ones exist. As an example might be mentioned, the disappearance of the placental circulation which on account of its large arteriovenous communication has been held a competent cause of the increased blood volume and increased venous pressure in the lower extremities,[4] and hence perhaps a factor in fluid retention. It was hoped that by administering large quantities of the estrogens or progesterone in the puerperium, concentrations of these substances characteristic of pregnancy might be maintained. Should, under these circumstances, the post-partum diuresis and sodium loss be prevented or delayed, the association of the original salt and water retention with the hormones of the placenta would be more or less established.

b. Hormones During Pregnancy.—The use of estrogens and progesterone has been suggested for the treatment of toxemia of pregnancy.[45, 55] Yet the patient with toxemia is already suffering from an abnormal retention of sodium and water. Should further salt retention follow hormone administration, such therapy might actually be dangerous.

Methods

The women studied were all patients hospitalized on the New York University obstetrical service in Bellevue Hospital. Diets were prepared, as previously described by a special dietitian in a small kitchen adjacent to the ward. The daily intake of sodium was fixed at 2.37 Gm. a low figure being used because this was thought advisable in patients with toxemia of pregnancy. Although the food was weighed to give approximately the sodium content desired, actual measurements were carried out by analysis of a duplicate twenty-four-hour sample diet on every fourth day, at which time slight changes in composition but not in sodium content were made.

All urine, feces, lochia, amniotic fluid, and blood lost at delivery were collected and sent to the laboratory. Details of the manner of collection and of the analytical procedures have been previously described.[48] Estrogens, pregnanediol and prolan (chorionic gonadotropin) were also measured on the urine specimens. The effect of the administration of the estrogens and progesterone on the hormone pattern of the urine will not, however, be reported here.

Clinical Material

The data obtained from five previously reported patients (Cases 1 to 5), whose sodium balances were studied during late pregnancy and the early puerperium without hormone administration were used as controls.[48] In contrast there are to be reported 5 patients who received hormones, either estrogen or progesterone, immediately after delivery in an effort to prevent or modify the sodium loss and diuresis of the early puerperium. In 3 of these patients large doses of hormones were also given during pregnancy to determine whether the sodium balance was in any way disturbed by such treatment.

Results

The sodium balance of the 5 hormone treated patients (Tables I, II, III, IV, and V) showed, with certain exceptions to be noted, the gen-

eral trends observed in the cases previously reported. These consist in a constant retention of sodium until the time of delivery with a negative balance appearing after parturition and reaching its greatest magnitude from the third to the fifth day. The days of greatest sodium loss correspond in general with the return of the urinary estrogen to nonpregnant levels. Summaries of the results of the balance studies are given in Table VI and in three graphs.

TABLE VI. SUMMARY OF SODIUM BALANCE OF FIRST TEN POST-PARTUM DAYS IN RELATION TO HORMONE ADMINISTRATION

NO.	PATIENT'S INITIALS	AGE	GRAVIDITY	WEEK OF DELIVERY	DIAGNOSIS	HORMONE THERAPY	GAIN OR LOSS OF SODIUM IN GRAMS FROM THE DAY BEFORE DELIVERY TO THE TENTH POSTPARTUM DAY
1	M. M.	17	ii	Term	Normal	0	− 4.00
2	M. C.	36	ii	Term	Normal	0	− 6.59
3	M. P.	17	i	Term	Normal	0	− 4.08
4	L. D.	20	i	Term	Toxemia	0	− 17.34
5	M. A.	25	i	36	Dead fetus. Toxemia	0	− 2.56 [− 19.44]
6	M. M.	22	ii	Term	Normal	Estradiol benzoate	+ 2.78
7	F. P.	22	iv	Term	Toxemia	Estradiol benzoate	− 7.34
8	R. Y.	20	i	Term	Normal	Estradiol	− 1.85
9	H. L.	21	i	Term	Normal	Progesterone	− 2.34
10	A. Z.	20	i	Term	Toxemia	Progesterone	− 3.77

1. Effect of Administration of Hormones in the Early Puerperium.— Attempts to maintain in the puerperium levels of estrogen or progesterone characteristic of pregnancy failed, if one may judge from the assay of the urine specimens collected during those days. Under normal conditions the concentration of estrogen in the urine falls rapidly and immediately after delivery and a level characteristic of the nonpregnant woman is reached on the third, fourth, or fifth day. Daily injection of 30,000 rat units of estradiol benzoate or 5 mg. of estradiol failed to alter this post-partum decline in urine estrogen values to any extent. No change in the rate of decline of urinary pregnanediol was brought about by the use of 50 mg. of progesterone daily. Nevertheless, for two reasons it appears that the amounts given were physiologically effective. With due regard to body weight relationships, the dosage of both estradiol and progesterone was comparable with that by which Thorn and Engel[51] obtained measurable effects on sodium excretion in dogs. It was further noteworthy that in none of the women treated by hormones in the puerperium was there any appreciable lactation.

Hormone Administration After Normal Pregnancy: In Chart 1 is shown the sodium balance for ten days before and ten days after delivery in six normal pregnancies, the eleventh ante-partum day being taken as the base line in each case. The first graph of the chart is a composite of balance studies previously reported on three normal untreated patients which serve as controls. The average loss of sodium

in the first ten post-partum days in these three patients was 4.89 Gm., the individual loss in each case being 4.00, 6.59, and 4.08 Gm., respectively (Table VI).

Each of the remaining three normal cases received estradiol benzoate, estradiol, or progesterone and in each sodium loss was less than in any of the three untreated patients. In Case 6 in whom a total of 300,000

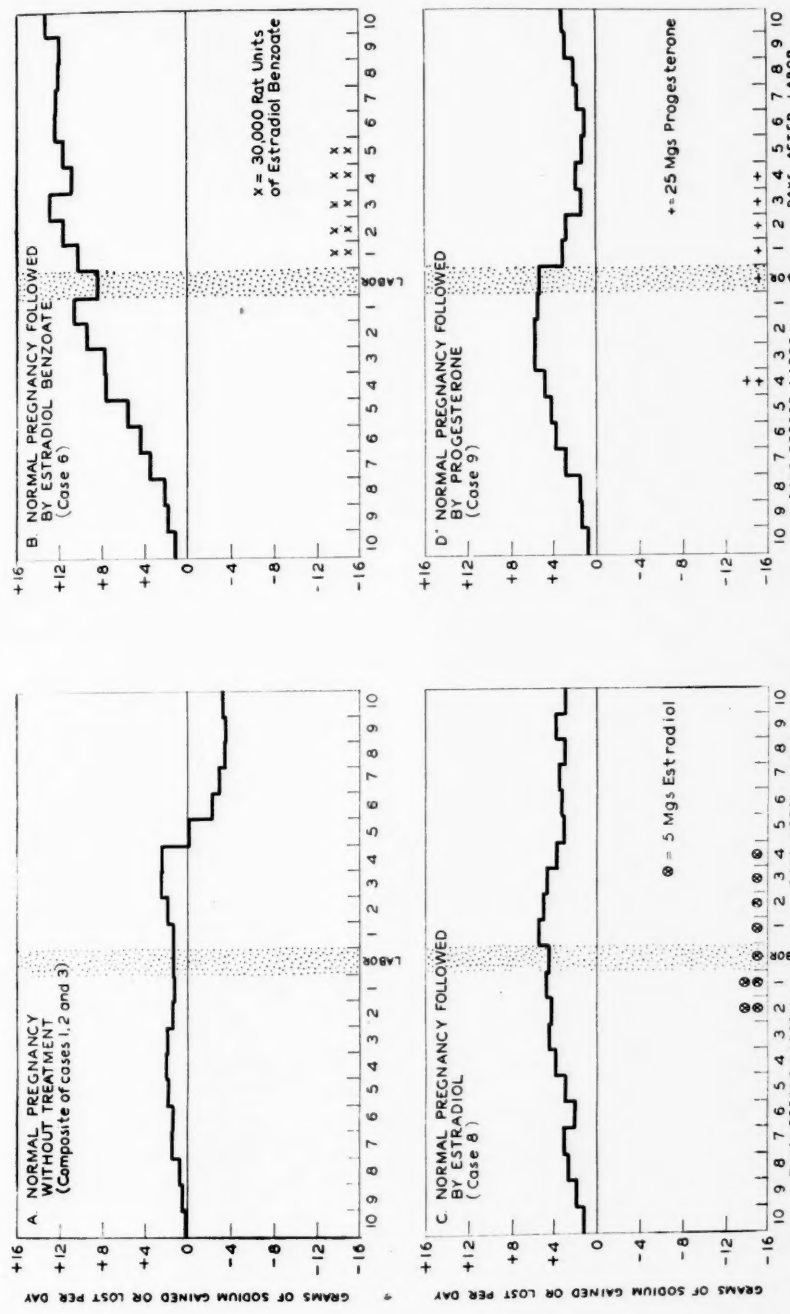
A NORMAL PREGNANCY WITHOUT TREATMENT (Composite of cases 1, 2 and 3)
B NORMAL PREGNANCY FOLLOWED BY ESTRADIOL BENZOATE (Case 6)
x = 30,000 Rat Units of Estradiol Benzoate
C NORMAL PREGNANCY FOLLOWED BY ESTRADIOL (Case 8)
⊗ = 5 Mgs Estradiol
D NORMAL PREGNANCY FOLLOWED BY PROGESTERONE (Case 9)
+ = 25 Mgs Progesterone
GRAMS OF SODIUM GAINED OR LOST PER DAY
DAYS BEFORE LABOR
DAYS AFTER LABOR
LABOR

Chart 1.—Effect of post-partum hormone administration on sodium balance after normal pregnancy.

rat units of estradiol benzoate was administered during the first five post-partum days, there was an actual retention of 2.78 Gm. of sodium before the tenth day. In Case 7 in whom 45 mg. of estradiol were given during the week beginning with the second day before delivery, there was a total loss of only 1.85 Gm. of sodium in the first ten post-partum days. Progesterone showed less evidence of being effectual, but

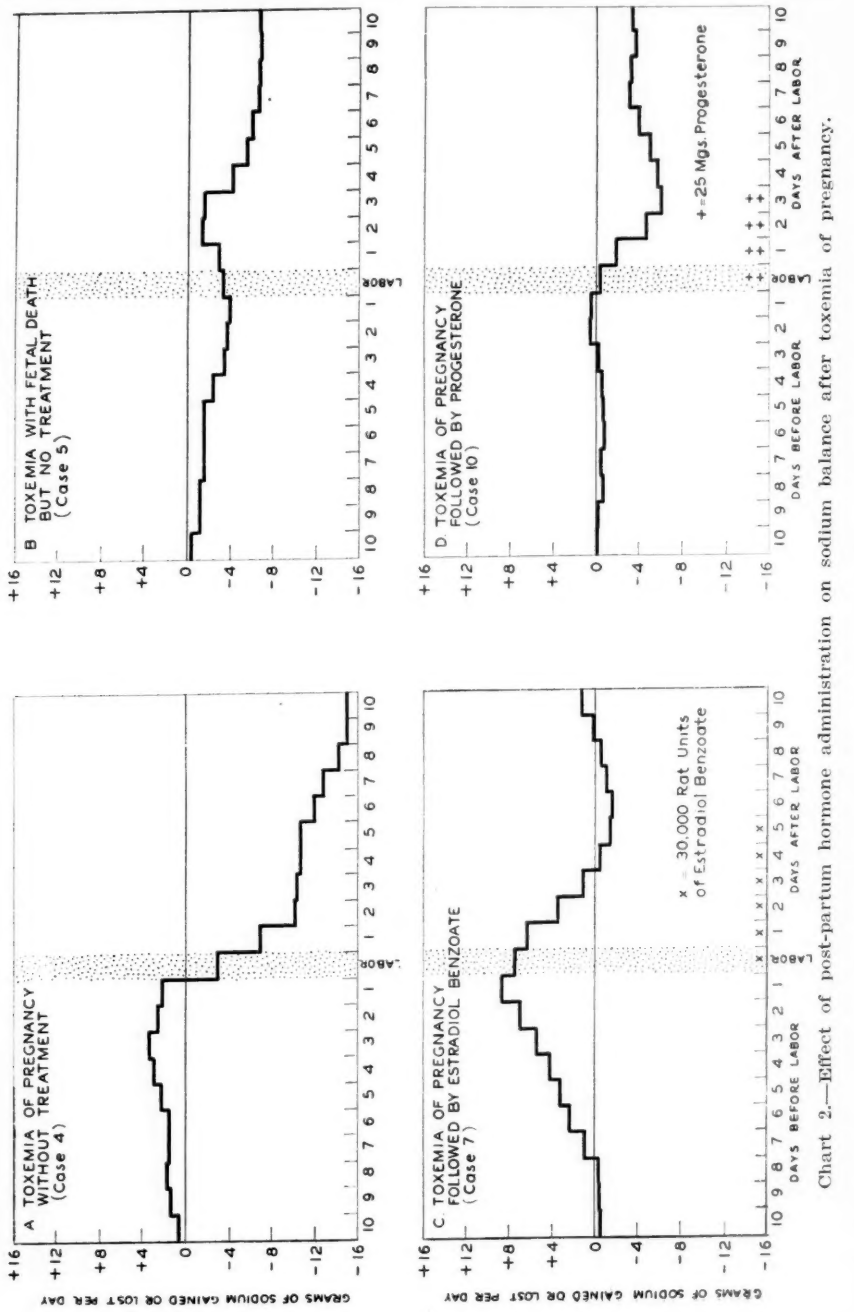
A TOXEMIA OF PREGNANCY WITHOUT TREATMENT (Case 4)
B TOXEMIA WITH FETAL DEATH BUT NO TREATMENT (Case 5)
C TOXEMIA OF PREGNANCY FOLLOWED BY ESTRADIOL BENZOATE (Case 7)
x = 30,000 Rat Units of Estradiol Benzoate
D TOXEMIA OF PREGNANCY FOLLOWED BY PROGESTERONE (Case 10)
+ = 25 Mgs. Progesterone
GRAMS OF SODIUM GAINED OR LOST PER DAY
DAYS BEFORE LABOR
DAYS AFTER LABOR
LABOR

Chart 2.—Effect of post-partum hormone administration on sodium balance after toxemia of pregnancy.

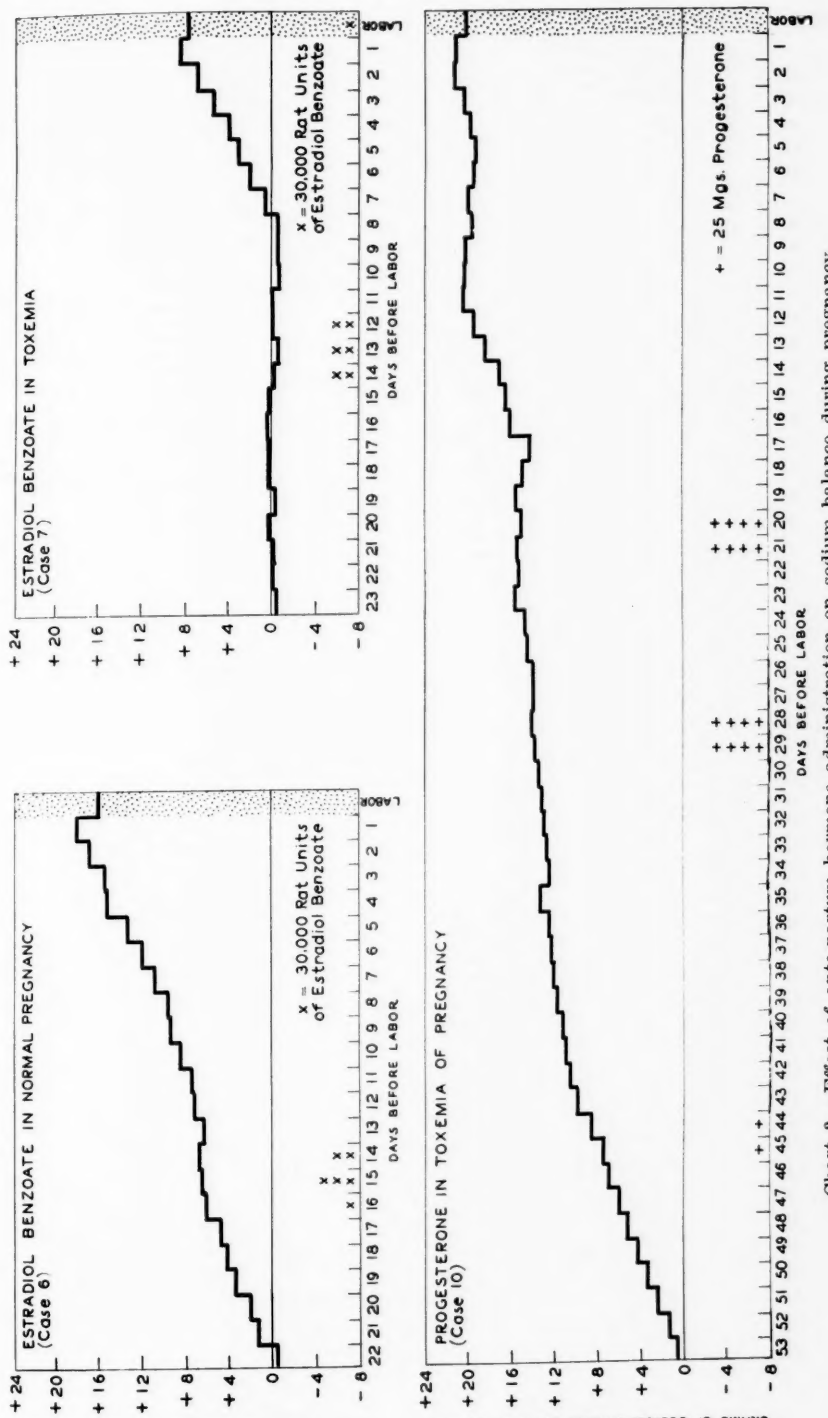
ESTRADIOL BENZOATE IN NORMAL PREGNANCY
(Case 6)
ESTRADIOL BENZOATE IN TOXEMIA
(Case 7)
PROGESTERONE IN TOXEMIA OF PREGNANCY
(Case 10)
x = 30,000 Rat Units of Estradiol Benzoate
+ = 25 Mgs. Progesterone
GRAMS OF SODIUM GAINED OR LOST PER DAY
DAYS BEFORE LABOR
LABOR

Chart 3.—Effect of ante-partum hormone administration on sodium balance during pregnancy.

when 125 mg. were given the loss of sodium before the tenth day was only 2.34 Gm.

Hormone Administration After Toxemia of Pregnancy: The water and sodium lost after toxemia of pregnancy are subject to great variations, depending principally on the amount of previous edema. The problem of setting up controls for studies of sodium loss in these cases is therefore much greater than after normal pregnancy. In Chart 2 is shown the sodium balance before and after delivery in four cases with toxemia of pregnancy. In Case 4, the loss in ten days amounted to 17.34 Gm. of sodium. In Case 5, the ten-day loss amounted to only 2.56 Gm., but this patient had begun to lose sodium, probably as an accompaniment of impending intrauterine fetal death, three weeks before her delivery. If the sodium loss in this case were taken from the day in which a negative balance set in and were carried to the tenth post-partum day, the total loss would amount to 19.44 Gm.

In the two remaining patients, hormone administration was begun on the day of labor and in each the sodium loss was lower than in either of the other cases of toxemia. In Case 7, receiving 300,000 units of estradiol benzoate, 7.34 Gm. were lost, while in Case 10, receiving 200 mg. of progesterone, the loss was 3.77 Gm. of sodium. In each untreated case the balance was still negative on the tenth post-partum day, while in each treated case sodium was again being retained.

2. Effects of Administration of Hormones During Pregnancy.—In three cases hormones were administered before the end of pregnancy to determine whether sodium excretion could be influenced under these conditions. The results can be found in detail in the tables and are shown graphically in Chart 3.

Attempts to influence the course of pregnancy by the administration of any of the sex hormones have, to the present time, met with only doubtful success. The reason for this is probably to be found in the fact that the amount of hormone administered has usually represented a very small fraction of the amount being constantly manufactured by the patient herself. The fairly large doses of estrogen and progesterone given to the patients of this study during their pregnancy may also have represented an insignificant increase over their normal supply.

A normal patient (Case 6) received 180,000 rat units of estradiol benzoate distributed over a three-day period, beginning sixteen days before the onset of labor. A patient with toxemia (Case 7) received the same dosage, beginning fourteen days before her delivery. In each instance there were several days of slightly decreased sodium retention followed by a slightly increased positive balance. Case 10, a patient with toxemia, received progesterone on three separate occasions, in doses of 50 to 200 mg. given over forty-eight-hour periods. On none of these occasions was the sodium balance in any way affected. The urine volume likewise did not change in any consistent manner following these injections.

Discussion

The absence of the post-partum sodium loss in one and its apparent reduction in another case of normal pregnancy after estrogen treatment in the puerperium is additional evidence that one of the causes of sodium and water retention in normal pregnancy is the high estrogen concentration characteristic of the body fluids during that period. That

progesterone may contribute to this is suggested by the case treated by this substance in which the loss of sodium in the early puerperium was relatively slight. The effect of estrogens and progesterone in preventing diuresis and sodium loss in the puerperium of patients who had had toxemia of pregnancy was less convincing but still suggestive.

The many factors which have been offered to explain the edema of pregnancy require a re-evaluation in the light of these effects of the sex steroids on sodium and water.

a. The ingestion of large quantities of sodium in the form of sodium chloride may increase the symptoms of toxemia, as de Snoo and Strauss have pointed out. The increase of extracellular water when sodium is administered is not, however, a peculiarity of pregnancy, but will occur to some degree in quite normal persons. That which is characteristic of both normal and toxemic pregnancy is the delayed elimination of sodium, so that a given quantity will be the cause of a greater degree of edema than in the nonpregnant person. To agree that excessive sodium retention is the immediate cause of the edema allows one, however, simply to transfer the problem to the cause of this increased tendency to sodium retention. The reasons for believing that the estrogens and progesterone are the cause of this physiologic change have been given.

b. A decrease in colloid osmotic pressure due to a reduction in plasma proteins may slightly increase the tendency to edema in the latter part of normal pregnancy. In exceptional cases with pronounced nutritional deficiencies a very low concentration of plasma protein may even be the major cause of the edema, but such cases are neither examples of normal pregnancy nor of pre-eclampsia. Dieckmann's[16] studies appear to have more or less disposed of the low plasma proteins as a primary or important contributing factor in the ordinary case of toxemia of pregnancy.

c. Although Dieckmann[16] has cited various observations suggesting that in normal pregnant patients "the renal function is altered if not actually temporarily impaired," the evidence for this point of view seems to us quite inconclusive. Studies of the last few years[7, 12, 54] based on the renal clearance of inulin and diodrast indicate no disturbance in kidney function in normal pregnancy. The normal glomerular filtration rate as determined by the inulin clearance in particular makes it extremely unlikely that a decreased renal function contributes in any way to the moderate edema characteristic of normal pregnancy. In some patients with toxemia of pregnancy, it is true, there is evidence of a moderate reduction in the glomerular filtration rate.[12, 18, 53] This might contribute slightly to the tendency to retain water, but the observed degree of reduction in this function would be wholly inadequate to produce any significant edema in the nonpregnant patient. It is further noteworthy that in a few of our toxemic patients in whom edema was present, the filtration rate was found to be quite normal. Such observations strongly suggest that the edema of both normal and toxemic pregnancy has an extrarenal cause.

d. In normal pregnant women some evidence for an increased capillary permeability has been found in various indirect tests which are said to have shown an increase in protein in the subcutaneous fluids.[33, 38] Agreement on this point is, however, not complete.[29] On the other hand

strong evidence against an increased capillary permeability in normal pregnancy exists in the absence of proteinuria, for were there any general tendency to capillary injury this should affect the glomerular capillaries and protein should appear in the urine. In the toxemic patient, however, the characteristic development of proteinuria indicates an increased glomerular permeability to the plasma proteins. Such a change may well affect the capillaries more or less universally and might be the explanation of the great increase in fluid retention which takes place when the normally pregnant woman becomes toxemic as well.

e. An increase in venous pressure, which is present in the veins of the legs during pregnancy,[4] undoubtedly favors the appearance of edema in the feet and ankles. This increased venous pressure in the legs may be due in part to the pressure of the large uterus on the vessels of the pelvis, in part to the structure of the placental circulation, in which a capillary bed is largely absent and conditions are thought to approximate those found in arteriovenous fistula.[5] The increased blood volume has also been ascribed by Burwell[5] to certain peculiarities of the placental circulation. The water of the lower extremities and that accounted for by the increased blood volume may represent a significant part of the total retained in normal pregnancy.

f. The general tendency of normal pregnant women to retain sodium and water appears, however, to be best explained by the fact that they are constantly under the influence of enormous quantities of the steroid sex hormones. This effect is so predictable from the known physiologic properties of these substances that were the tendency to sodium and water retention not present, one would have to find an explanation for its absence.

The increase in the tendency to sodium and water retention which takes place with the onset of toxemia does not, however, find a complete explanation on the basis of a further rise in hormone effectiveness. The sudden appearance of proteinuria and of hypertension and the change from hydremia toward hemoconcentration indicates that a new mechanism is at work. Furthermore, in most cases of preeclampsia, rates of steroid sex hormone excretion are not increased, but probably decreased. Although the estrogens and progesterone probably continue to contribute to the sodium retention in toxemia, the greater edema of that disease cannot be considered simply an exaggeration of that found in normal pregnancy.

During pregnancy the administration of what would now be regarded from the clinical standpoint as large doses of estrogen and progesterone had no demonstrable effect on sodium balance. It is believed that in relation to the enormous quantities of hormone produced daily by the pregnant woman the administered quantities were actually small, perhaps physiologically insignificant.

Conclusions

1. Among several factors which cause normal pregnant women to develop edema, the most important is probably the physiologic influence of the estrogens and progesterone on the excretion of sodium and water.

2. In the edema of specific toxemia, additional factors are almost certainly at work. Yet it is important to take into account the fact

that when the pregnant woman develops toxemia she is already physiologically conditioned to retain water readily. In this indirect sense at least the estrogens and progesterone may contribute greatly to the clinical manifestations and course of the disease.

References

1. Albers, H.: Zentralbl. f. Gynäk. **63**: 1377, 1939.
2. Astwood, E. B.: Endocrinology **23**: 25, 1938.
3. Aykroyd, O. E., and Zuckerman, S.: J. Physiol. **94**: 13, 1938.
4. Burwell, C. S.: Ann. Int. Med. **11**: 1305, 1938.
5. Idem: Am. J. M. Sc. **195**: 1, 1938.
6. Cantarow, A., and Rakoff, A. E.: Endocrinology **27**: 652, 1940.
7. Chesley, L. C., and Chesley, E. R.: Am. J. Physiol. **127**: 731, 1939.
8. Idem: Am. J. Obst. & Gynec. **42**: 976, 1941.
9. Clarke, R. W.: Am. J. Physiol. **123**: 39, 1938.
10. Idem: Am. J. Physiol. **131**: 325, 1940.
11. Coons, C. M., Schiefelbusch, A. T., Marshall, G. B., and Coons, R. R.: Oklahoma Agricultural and Mechanical College, Agric. Exper. Station Bull. 223, 1935.
12. Corcoran, A. C., and Page, I. H.: Am. J. M. Sc. **201**: 385, 1941.
13. Crawford, M. D.: J. Obst. & Gynaec. Brit. Emp. **47**: 63, 1940.
14. Dieckmann, W. J.: Am. J. Obst. & Gynec. **26**: 543, 1933.
15. Idem: Am. J. Obst. & Gynec. **32**: 927, 1936.
16. Idem: Am. J. Obst. & Gynec. **41**: 1, 1941.
17. Dieckmann, W. J., and Wegner, C. R.: Arch. Int. Med. **53**: 71, 188, and 353, 1934.
18. Dill, L. D., Isenhour, C. E., Cadden, J. F., and Schaffer, N. K.: Am. J. Obst. & Gynec. **43**: 32, 1942.
19. Feldman, H., Van Donk, E. C., Steenbock, H., and Schneiders, E. F.: Am. J. Physiol. **115**: 69, 1936.
20. Fisher, R. B., and Zuckerman, S.: J. Physiol. **89**: 15, 1936.
21. Freyberg, R. H., Reekie, R. D., and Folsome, C.: Am. J. Obst. & Gynec. **36**: 200, 1938.
22. Friedlander, M., Laskey, N., and Silbert, S.: Endocrinology **19**: 342, 1935.
23. Idem: Endocrinology **19**: 461, 1935.
24. Idem: Endocrinology **20**: 329, 1936.
25. Guthkelch, A. N., and Zuckerman, S.: J. Physiol. **91**: 269, 1937.
26. Harding, V. J., and Van Wyck, H. B.: J. Obst. & Gynaec. Brit. Emp. **33**: 17, 1926.
27. Idem: Canad. M. A. J. **24**: 635-640, 1931.
28. Idem: Am. J. Obst. & Gynec. **24**: 820, 1932.
29. Hellmuth, K.: Zentralbl. f. Gynäk. **46**: 290, 1922.
30. Janney, J. C., and Walker, E. W.: J. A. M. A. **99**: 2078, 1932.
31. Keith, N. M., Rowntree, L. G., and Geraghty, J. T.: Arch. Int. Med. **16**: 547, 1915.
32. Krohn, P. L., and Zuckerman, S.: J. Physiol. **88**: 369, 1937.
33. Lash, A. F.: Surg., Gynec. & Obst. **43**: 40, 1926.
34. Lundin, H., and Scharf, R.: J. Metabol. Research. **8**: 259, 1926.
35. McManus, M. A., Riley, G. A., and Janney, J. C.: Am. J. Obst. & Gynec. **28**: 524, 1934.
36. Oberst, F. W., and Plass, E. D.: Am. J. Obst. & Gynec. **31**: 61, 1936.
37. Idem: J. Lab. & Clin. Med. **26**: 664, 1941.
38. Petersen, W. F., and Lash, A. F.: Arch. Int. Med. **39**: 12, 1927.
39. Plass, E. D., and Bogert, L. J.: Johns Hopkins Hosp. Bull. **35**: 361, 1924.
40. Plass, E. D., and Matthew, C. W.: Am. J. Obst. & Gynec. **12**: 346, 1926.
41. Rupp, H.: Ztschr. f. Geburtsh. u. Gynäk. **95**: 383, 1929.
42. Schwarz, O. H., and Dieckmann, W. J.: Am. J. Obst. & Gynec. **18**: 515, 1929.
43. Selye, H., and Bassett, L.: Proc. Soc. Exper. Biol. & Med. **44**: 502, 1940.
44. Skajaa, K.: Acta obst. et gynec. Scandinav. **8**: 371, 1929.
45. Smith, G. V., and Smith, O. W.: J. Clin. Endocrinology **1**: 477, 1941.
46. Strauss, M. B.: Am. J. M. Sc. **194**: 772, 1937.
47. Talbot, N. B., Lowry, O. H., and Astwood, E. B.: J. Biol. Chem. **132**: 1, 1940.
48. Taylor, H. C., Jr., Warner, R. C., and Welsh, C. A.: Am. J. Obst. & Gynec. **38**: 748, 1939.
49. Thompson, H. E., Jr., and Pommerenke, W. T.: J. Nutrition **17**: 383, 1939.

50. Thomson, K. J., Hirsheimer, A., Gibson, J. G., and Evans, W. A., Jr.: Am. J. Obst. & Gynec. **36**: 48, 1938.
51. Thorn, G. W., and Engel, L. L.: J. Exper. Med. **68**: 299, 1938.
52. Thorn, G. W., Nelson, K. R., and Thorn, D. W.: Endocrinology **22**: 155, 1938.
53. Wellen, I., Welsh, C. A., and Taylor, H. C., Jr.: J. Clin. Investigation **21**: 63, 1942.
54. Welsh, C. A., Wellen, I., and Taylor, H. C., Jr.: J. Clin. Investigation **21**: 56, 1942.
55. White, P., and Hunt, H.: J. A. M. A. **115**: 2039, 1940.
56. Zuckerman, S., Palmer, A., and Bourne, G.: Nature **143**: 521, 1939.

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ANTECUBITAL AND FEMORAL VENOUS PRESSURE IN NORMAL AND TOXEMIC PREGNANCY*

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INTEREST in venous pressure in pregnancy has been aroused by the recent reports of Burwell and his collaborators[1-3] dealing with a variety of vascular and cardiac phenomena in the pregnant woman. These workers confirmed the earlier findings of Runge,[4] who had demonstrated a considerable elevation of venous pressure in the lower extremities in the latter part of pregnancy, and they suggested that the abnormal venous pressure, as well as other disturbances in vascular physiology, might be explained on the basis of the fact that the placental circulation simulates an arteriovenous shunt. If it can be shown that the level of venous pressure is such as to impair normal fluid exchange in the arteriolar and venous limbs of the capillaries, the appearance of edema in pregnancy should be readily explainable. More remotely, such an effect on fluid movement might be given consideration as a factor in the development of the toxemias of pregnancy.

However, the numbers of venous pressure determinations in pregnancy thus far reported are insufficient to permit drawing final conclusions. The purpose of the present study was to establish standard values for venous pressure in both upper and lower extremities throughout pregnancy and in the immediate puerperium. For comparison with these figures it seemed desirable to obtain a series of determinations on patients suffering from the various forms of the hypertensive toxemias of pregnancy, particularly in view of the fact that the literature contains contradictions as to the levels of antecubital venous pressure during pregnancy toxemia and the further fact that no observations have been made of venous pressure in the lower extremities during toxemic episodes. Finally, in an attempt to throw further light on the

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nature of the mechanism responsible for the elevation of venous pressure below the level of the pregnant uterus, the portions of the study dealing with pelvic tumors, intrauterine fetal death, and venous pressure during delivery were carried out.

Review of Literature

Comparatively few studies of venous pressure during pregnancy have been made and most of them are concerned only with pressure in the veins of the upper extremity. While Runge[4] commonly receives credit for making the first such observations, Fuchs[5] published a few inconclusive determinations of venous pressure in pregnancy three years earlier. Runge observed venous pressure directly by the method of Moritz and von Tabora[6] in 34 normal pregnant women, 7 post-partum patients, and 6 essentially normal gynecologic patients. The average pressure in the saphenous vein was slightly elevated prior to the seventh month of gestation and was decidedly elevated during the last trimester. In 16 patients observed during the tenth lunar month, the venous pressures in the legs ranged from 10.7 to 31.4 cm. of water, with an average value of 20.3 cm. of water. Runge suggested that the increased pressure in the lower extremities during pregnancy resulted from the increased quantities of blood returning through the pelvic veins to the main venous trunks rather than from simple mechanical compression of large veins by the growing uterus.

Kaboth[7] found the arm venous pressure to be slightly elevated in the last half of pregnancy, and in two patients with eclampsia and edema the venous pressure ranged from 16 to 25 cm. of water. Villaret, Saint-Girons and Salasc[8] measured both arm and leg (saphenous vein) pressures with an aneroid manometer in five pregnant women "near term"; the ranges were 12 to 15 cm. in the arm and 31 to 42 cm. of water in the leg. Dellepiane[9] found that the venous pressure in the arm during normal pregnancy ranged from 10 to 16 cm. of water, while immediately post partum it was 18 to 22 cm. of water.

Krukenberg[10] reported that the average venous pressure in the arm in 29 normal pregnant women was 5.69 cm. of water. Baráth and Weiner[11] obtained venous pressure readings on 11 pregnant patients without edema and plotted them against colloid osmotic pressure values for the same individuals. From their graph it appears that the venous pressures in the arm ranged from 11 to 18 cm. of water, while 11 normal individuals had venous pressures ranging from 4 to 7 cm. of water. Strauss[12] determined directly the venous pressures in the arms of 20 normally pregnant women during the last two months of gestation. The values ranged from 3 to 18 cm. of water and the average was 10 cm. For comparison, 20 pregnant patients in the last trimester, with arterial blood pressures of 150/100 mm. Hg or higher, had venous pressures ranging from 8 to 20.5 cm. of water, averaging 13.3 cm. From these observations Strauss concluded that arm venous pressure often was above the upper limits of normal in uncomplicated pregnancy and was commonly elevated to abnormal levels in pregnancy toxemias.

Róna[13] reported 53 values for cubital vein pressure during the last trimester of pregnancy. They ranged from 3.0 to 19.4 cm. of water and averaged 10.4 cm. The arterial blood pressures of some of these patients fell in the "toxemia" range. Twenty-two values for venous pressure in leg veins ranged from 3.7 to 29.3 cm. of water and averaged

18.1 cm. Landt and Benjamin[14] made repeated venous pressure observations on 19 women who were followed throughout pregnancy and the puerperium. They concluded that arm venous pressure was moderately high in early pregnancy, decreased slightly until the end of the sixth or seventh month, and then rose gradually until delivery occurred. The range of values was 4.8 to 11.0 cm., and it was pointed out that all of the values fell in the "normal range." Cohen and Thomson[15] made 41 observations of arm venous pressure in ten patients; five observed ante partum had a range of venous pressure from 4 to 12 cm. of water and five post-partum patients had pressures from 6.4 to 12 cm. Luisi[16] found that 13 normally pregnant women had venous pressures ranging from 1.8 to 15.0 cm. of water, while 29 subjects with various types of pregnancy toxemia had a venous pressure range of 2.0 to 14.5 cm. of water. He concluded that venous pressure in the arm increases during normal pregnancy, that the increase is more marked during parturition and in the few hours after delivery, and that it returns to normal during the puerperium.

Perhaps the most important contribution to the subject of venous pressure in pregnancy has been that of Burwell and his co-workers.[1-3] Their preliminary studies indicated that in nonpregnant persons without heart disease or local venous obstruction, venous pressures measured with the subject lying in bed were of the same general magnitude in the arm and in the leg (femoral vein). In 24 observations of both antecubital and femoral venous pressures in 22 pregnant women from the third month of gestation to term, the arm values ranged from 5.1 to 15.6 cm. of water and the femoral vein pressures from 7.8 to 26.5 cm. of water. It appeared that there was an abnormal rise in femoral venous pressure by the beginning of the second trimester of pregnancy, and that this elevation persisted and even increased throughout pregnancy. After delivery the femoral venous pressures returned to normal levels. Burwell and others[3] also observed pressures in jugular, femoral, and uterine veins of 12 pregnant bitches. With the animals supine and under barbital anesthesia it was found that the pressures in the femoral veins were higher than those in the jugular veins. This difference in pressure was diminished or absent after the uterus was removed. Opening the abdominal cavities of the pregnant animals did not appreciably lower the femoral venous pressures. Lifting the gravid uterus from its normal position and supporting it in such a way that it no longer pressed on the large veins produced a fall in femoral pressure but the latter usually remained above the pressure in the jugular vein. After the uterus was surgically removed the femoral venous pressure approached that in the jugular vein in 5 of 6 animals in which comparative measurements were made. In six pregnant bitches pressure determinations were made in broad ligament veins which presumably drained uterine wall and placental site; these uniformly exhibited higher pressures than the femoral veins. In nonpregnant, anesthetized dogs distended by injecting physiologic solution of sodium chloride into their abdominal cavities it was noted that the abdominal wall was tense when femoral venous pressure reached a level comparable to that in pregnant animals. But, since the abdominal wall of the pregnant bitch or pregnant woman is not tense even in the presence of a markedly elevated femoral venous pressure, it was concluded that the elevated femoral venous pressure observed during pregnancy is not the result of an increase in intra-abdominal pressure.

During a study of blood volume in pregnancy, Thomson, Hirsheimer, Gibson and Evans[17] determined directly arm venous pressures in 15 normal pregnant women at various stages of gestation. Their range of values was 2.5 to 11.3 cm. of water. Thomson, Reid and Cohen[18] have reported a series of arm venous pressure determinations in normal pregnant women, pregnant women with compensated and decompensated heart disease, and in women with toxemias of pregnancy. In twenty normal pregnant women 65 ante-partum values and 29 post-partum values fell in the normal range. They stated that the average venous pressure values were slightly higher in early pregnancy than in mid and late pregnancy and the puerperium. It was noted that 9 of 15 observations made during the first two weeks of the puerperium were higher than the corresponding final ante-partum values. Venous pressure in 27 compensated cardiac patients throughout pregnancy and the puerperium fell within normal limits, while 18 patients who developed cardiac failure during pregnancy also exhibited arm pressures within the normal range, except in one instance where there was massive edema. However, where pre- and post-failure observations were made, the venous pressure was higher when there were signs of heart failure. In 21 women with toxemia of pregnancy the venous pressure values did not exceed 14 cm. of water, which these workers considered the extreme upper limit of normal, but more of the toxemia values fell in the upper normal range than did values in the nontoxemic pregnant group.

Veal and Hussey[19] have studied the venous circulation in the lower extremities during pregnancy by measuring venous pressure directly in the popliteal vein while the patient was standing. These workers have used an "exercise test" in an attempt to demonstrate that women with edema or varicosities have more severe venous obstruction than those without such phenomena. It is their belief that ordinary measurements of femoral venous pressure fail to demonstrate this difference, since the venous system may be adequate during rest and inadequate with activity.

Hamilton and Thomson's monograph[20] on the heart in pregnancy contains a reference to 7 observations of ante-partum femoral venous pressure which varied between 12.5 and 25.0 cm. of water. The other values mentioned in this work were taken from the paper of Thomson, Reid and Cohen.[18] In their monograph on pre-eclamptic and eclamptic toxemia, Dexter and Weiss[21] have noted that the arm venous pressure in 9 normal pregnant women without edema, albuminuria, or hypertension averaged 10.4 cm., and in 18 patients with edema and various types of toxemia, the average was 10.1 cm. of water. On the basis of these observations they concluded that variations in venous pressure were not related to degrees of edema, hypertension, or albuminuria, and that hydrostatic pressure in the capillaries played no essential part in the formation of the edema of pregnancy.

In summary, 8 reports list values for arm venous pressures in pregnancy which are in excess of 14 cm. of water, a value which is frequently spoken of in the general literature as being the extreme upper limit of normal. The values in the other eight reports dealing with arm pressures fall into the so-called normal range. Of the five reports which include determinations made in patients with toxemia of pregnancy, all indicate that the arm venous pressure values *may* lie above normal limits, although this specific conclusion was reached by only two of the authors. There are 7 reports on venous pressure in the lower extremity and all indicate that the values are elevated above normal

during pregnancy. Only two investigators have attempted to demonstrate a gradient of pressure in the leg as pregnancy advanced, and the numbers of observations reported by them are too few to permit definite conclusions. There have been no observations on venous pressure in the lower extremity during pregnancy toxemia.

Apparatus, Material and Method

The apparatus used to determine venous pressure directly was essentially the same as that described originally by Moritz and von Tabora,[6] namely, a water manometer, a reservoir for saline solution connected to the manometer and to an intravenous needle by means of suitable rubber tubing and a Y-tube (replaced by a 3-way glass stopcock). The glass manometer tube had a bore of 2 mm. and was mounted on a wooden standard which could be adjusted vertically by means of a sliding central panel. A meter stick with a spirit level attached centrally along one edge served as a leveling device. The intravenous needles were 19-gauge, those used in the arm veins being 1½ inches long, those for the femoral veins 2½ inches. The apparatus was filled with a 1 per cent solution of sterile sodium citrate in physiologic saline for all except the prolonged observations on patients undergoing operations; for the latter a 3 per cent citrate solution was used.

Seven hundred fifty-seven determinations of venous pressure were made in 255 different subjects. Three hundred forty-five determinations were made in the antecubital vein and 412 in the femoral vein. Thirty of the subjects were normal controls, consisting of nurses and ambulatory patients from the gynecological service of the University of Minnesota Hospitals. One hundred fifty-eight subjects were normally pregnant women from the obstetrical services of the University of Minnesota Hospitals, the University of Virginia Hospital, and the Booth Memorial Hospital of St. Paul, observed during pregnancy and/or the puerperium in a total of 160 pregnancies. From the same sources there were 55 women with some form of hypertensive toxemia of pregnancy observed in 57 different pregnancies. Twelve patients with a variety of abdominopelvic tumors were from the gynecologic service of the University of Minnesota Hospitals.

All determinations were made on recumbent (supine) subjects who had rested in that position for at least ten minutes. In the arm the technique was essentially that advised by Lyons, Kennedy and Burwell.[22] Readings were made to the nearest 0.5 cm. except in the case of the control subjects, where readings were made to the nearest millimeter. If the column of fluid in the manometer fell unusually slowly or if the level at which it settled out was above the supposed upper limit of normal (i.e., 12 cm. of water), possible sources of error in the technique or in the positioning of the extremity were searched for and corrected.

In the lower extremity, the technique was similar to that described by Ferris and Wilkins.[23] Occasionally the femoral artery was entered accidentally; when this occurred the needle was removed from the thigh and the blood which had rapidly extended well above the level of the adapter was washed out. The needle then was reinserted somewhat more medially than at the first trial. At the conclusion of each determination, digital pressure was maintained at the venipuncture site for one or two minutes to prevent the formation of a hematoma. In the

prolonged observations on patients undergoing abdominal operations the needle was briefly flushed with solution from the reservoir at intervals of three to four minutes in order to prevent clotting of blood in the relatively small lumen. Manometer readings were recorded at intervals of one-half to five or ten minutes, depending upon the rapidity of the observed changes in venous pressure.

The statistical expressions were computed by the usual formulae, as given by Treloar.[24] When the probability of a difference between means being the result of an error of random sampling was open to question because of smallness of the sample (less than 30), the probability factor (P) was recalculated by Fisher's[25] small sample formula and table of "t" values.

Results

1. *Normal Controls.*—In 30 normal females, ranging in age from 13 to 48 years, the mean value for antecubital venous pressure in the supine posture was 7.88 cm. of water and for femoral venous pressure was 11.43 cm. of water. The respective standard deviations were 1.64 and 3.43 and the standard errors of the means were 0.31 and 0.64. The coefficient of variation was somewhat smaller for the arm pressure values, being 21 per cent, as compared with a coefficient of variation of 30 per cent for the femoral pressure measurements. The difference of 3.55 cm. of water between the mean values for antecubital and femoral venous pressure is statistically significant, since this difference is more than five times as great as its standard error (Table II, A).

2. *Normally Pregnant Subjects.*—In 158 normally pregnant or post-partum women observed in 160 pregnancies, 400 determinations of venous pressure were made, 261 of them ante partum and 139 post partum. The mean antecubital venous pressure in 114 ante-partum determinations was 7.72 ± 0.23 cm. of water and in 59 post-partum determinations was 8.03 ± 0.29 cm. of water. The difference between these two values is not statistically significant, as may be seen from the values for k and P in Table II, E. Nor do these mean pressures vary significantly from the normal control figure of 7.88 ± 0.31 cm. of water (Table II, B and F).

Because of the rising femoral venous pressure throughout the period of gestation, it was necessary in the interests of comparison to divide the arm and femoral pressure determinations into a number of small groups, as has been done in Table I. It will be noted that the ante-partum period has been divided into nine portions and the post-partum period into four.

While there are minor fluctuations in the mean values for antecubital venous pressure determined at various times ante partum and post partum, the range being 6.97 ± 0.39 to 10.75 ± 1.66 cm. of water, none of the group means is significantly different from the normal control value (see Table II, B) for nonpregnant individuals. Although there were a number of rather high individual values for antecubital pressure immediately post partum, it is not possible to demonstrate a significant post-partum elevation when the grouping of values is broadened to forty-eight-hour post-partum periods, as has been done in Tables I and II, B, and in Fig. 1.

The mean values for femoral venous pressure in the various gestational groups show a more or less constant upward trend throughout

TABLE I. MEANS, STANDARD DEVIATIONS AND STANDARD ERRORS OF MEANS FOR ANTECUBITAL AND FEMORAL VENOUS PRESSURE AT VARIOUS STAGES OF NORMAL AND TOXEMIC PREGNANCY

WEEKS OF GESTATION OR DAYS POST PARTUM	ANTECUBITAL VENOUS PRESSURE, CM. WATER				FEMORAL VENOUS PRESSURE, CM. WATER			
	NUMBER OF VALUES IN SAMPLE	MEAN	STANDARD DEVIATION	STANDARD ERROR OF MEAN	NUMBER OF VALUES IN SAMPLE	MEAN	STANDARD DEVIATION	STANDARD ERROR OF MEAN
A. Normal pregnancy								
5 - 12	7	7.85	1.93	1.02	7	9.14	3.54	1.45
13 - 16	7	8.07	3.56	1.46	7	14.00	7.69	3.14
17 - 20	5	7.60	3.20	1.60	5	14.60	3.78	1.89
21 - 24	11	8.95	2.31	0.73	15	17.83	3.28	0.88
25 - 28	4	10.75	2.87	1.66	6	21.00	2.57	1.15
29 - 32	10	7.15	2.27	0.76	12	22.29	2.76	0.83
33 - 36	19	6.97	1.64	0.39	27	21.33	4.09	0.80
37 - 38	9	7.11	2.85	1.01	18	22.94	3.89	0.94
39 - 40+	42	7.64	2.52	0.39	50	24.37	4.61	0.65
5 - 40+ (all ap.)	114	7.72	2.45	0.23				
1 - 2	16	8.91	2.69	0.69	26	10.08	1.81	0.36
3 - 4	16	7.94	1.97	0.51	21	9.64	2.53	0.57
5 - 9	21	7.59	2.19	0.49	27	9.04	2.43	0.48
10 - 20	6	7.42	2.14	0.96	6	10.00	3.86	1.73
3 - 20	43	7.70	2.03	0.31	54	9.38	2.60	0.35
1 - 20 (all pp.)	59	8.03	2.26	0.29	80	9.61	2.37	0.27
B. Toxemic pregnancy								
5 - 12	2	9.75			2	13.50		
13 - 16	1	5.50			1	8.00		
17 - 20	2	6.75			2	11.00		
21 - 24	2	9.50			2	14.25		
25 - 28	3	9.33	2.27	1.61	3	21.33	3.57	2.53
29 - 32	9	8.11	3.63	1.28	8	18.88	3.06	1.16
33 - 36	9	9.44	3.44	1.22	11	20.86	5.07	1.60
37 - 38	20	6.88	2.18	0.50	21	23.07	3.22	0.72
39 - 40+	24	8.75	3.91	0.82	27	22.22	4.86	0.95
5 - 40+	72	8.21	3.29	0.39				
1 - 2	9	12.39	4.01	1.42	10	13.05	4.38	1.46
3 - 20	17	8.59	3.55	0.89	23	9.22	2.59	0.55

pregnancy (Tables I and II, H, Figs. 2 and 3). While the mean pressure prior to the thirteenth week of pregnancy fell just below the control mean minus three standard errors, the means for all the subsequent gestational periods were clearly above the average for the controls. However, the numbers of individual measurements from thirteen to twenty weeks were small and their variations relatively great, with the result that a statistically significant difference between pregnant and nonpregnant femoral vein pressures was not demonstrated prior to twenty-one weeks (Table II, H). In the thirty-ninth and fortieth (or more) weeks of pregnancy, the mean femoral venous pressure was 24.37 ± 0.65 cm. of water (17.9 ± 0.47 mm. Hg). It fell abruptly following delivery, so that the mean value during the first forty-eight hours post partum was 10.08 ± 0.36 cm. of water, i.e., essentially that of the nonpregnant controls. The two subsequent post-partum groups, three to four and five to nine days, showed average pressures which were significantly lower than the controls (see Table II, H) while the

mean of the few remaining post-partum determinations (ten to twenty days) fell within the range of the control mean (11.43 ± 0.64 cm. H_2O). It may be noted in Table II, J, that the mean of all the post-partum femoral pressures in the normally pregnant subjects, as well as the mean of the values from the third to the twentieth day, was significantly less than that for the control group. The post-partum values were, respectively, 9.61 ± 0.27 and 9.38 ± 0.35 cm. of water.

3. *Pregnant Patients With Toxemia.*—Although it would be desirable to group these individuals according to the clinical variety of toxemia (i.e., low reserve kidney, pre-eclampsia, arteriolosclerotic toxemia), there were insufficient numbers of individuals in each category for separate statistical treatment. Furthermore, inspection of the data showed a similar range of values in each toxemic group, so that it seems reasonable to consider these pressures collectively. Since toxemia of pregnancy does not commonly make its appearance in the first half of gesta-

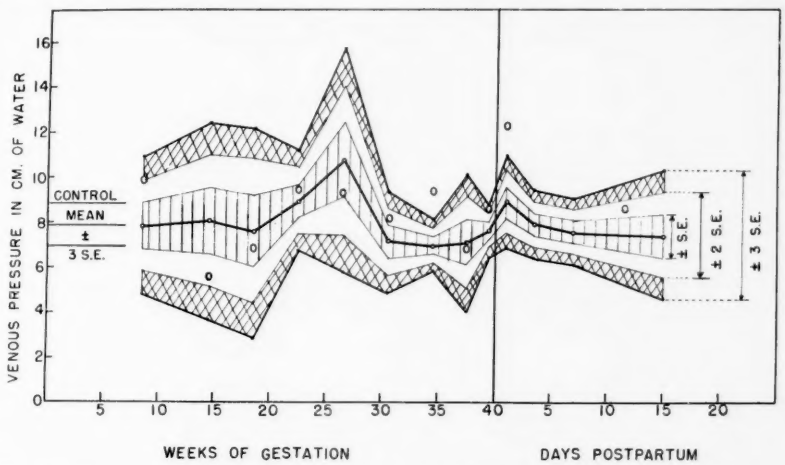

Fig. 1.—Showing the average course of antecubital venous pressure throughout normal and toxemic pregnancy and the immediate puerperium. The heavy central line is drawn through the mean values for normal pregnancy (see Table I) and the three zones on each side of the mean represent areas covered by the mean ± 1, 2 and 3 standard errors. The superimposed circles indicate mean values for toxemic pregnancies. At the left is shown the range of the mean value for nonpregnant controls.

tion, it was difficult, obviously, to collect sufficient numbers of pressure determinations in the early months to allow statistical analysis of the data. It will be noted in Table I that standard deviations for the toxemia patients were not computed prior to the twenty-fifth week of pregnancy and that the post-partum period was divided into only two instead of four groups. In 55 women with some form of hypertensive toxemia of pregnancy, 208 determinations of venous pressure were made, 149 of them ante partum and 59 post partum. Two patients were observed in two successive pregnancies. Fig. 1 demonstrates that the mean values for antecubital venous pressure in the toxemic individuals fell for the most part within the range of normally pregnant mean plus or minus three standard errors of the mean. The two exceptions were (1) the mean of the values from thirty-three to thirty-six weeks and (2) that of the first forty-eight-hour post-partum period. However, the statistical significance of these differences is open to question when

TABLE II. SIGNIFICANCE OF DIFFERENCES BETWEEN MEANS FOR ANTECUBITAL AND FEMORAL VENOUS PRESSURE AT VARIOUS STAGES OF NORMAL AND TOXEMIC PREGNANCY, INCLUDING THE PUERPERIUM. PRESSURE IN CM. OF WATER

GROUP	MEAN (1) ± S. E.	NO. OF VALUES IN SAMPLE	MEAN (2) ± S. E.	NO. OF VALUES IN SAMPLE	DIFFERENCE BETWEEN MEANS (1) AND (2)	S. E. OF DIFF.	R (k)*	P†
A. Antecubital Controls (1) vs. Femoral Controls (2)								
All	7.88 ± 0.31	30	11.43 ± 0.64	30	3.55	0.706	5.03	0.000,000,6
B. Antecubital Controls (1) vs. Normal Pregnancy (2)								
5-12 wk. ap.	7.88 ± 0.31	30	7.85 ± 1.02	7	0.03	1.067	0.02	0.984
13-16	7.88 ± 0.31	30	8.07 ± 1.46	7	0.19	1.493	0.13	0.897
17-20	7.88 ± 0.31	30	7.60 ± 1.60	5	0.28	1.630	0.17	0.865
21-24	7.88 ± 0.31	30	8.95 ± 0.73	11	1.07	0.793	1.35	0.117
25-28	7.88 ± 0.31	30	10.75 ± 1.66	4	2.87	1.688	1.70	0.089
29-32	7.88 ± 0.31	30	7.15 ± 0.76	10	0.73	0.821	0.89	0.374
33-36	7.88 ± 0.31	30	6.97 ± 0.39	19	0.91	0.498	1.83	0.067
37-38	7.88 ± 0.31	30	7.11 ± 1.01	9	0.77	1.058	0.73	0.465
39-40+	7.88 ± 0.31	30	7.64 ± 0.39	42	0.24	0.498	0.48	0.631
1-2 days pp.	7.88 ± 0.31	30	8.91 ± 0.69	16	1.03	0.756	1.36	0.174
3-4	7.88 ± 0.31	30	7.94 ± 0.51	16	0.06	0.596	0.10	0.920
5-9	7.88 ± 0.31	30	7.59 ± 0.49	21	0.29	0.579	0.50	0.617
10-20	7.88 ± 0.31	30	7.42 ± 0.96	6	0.46	1.010	0.46	0.646
5-40+ wk. ap.	7.88 ± 0.31	30	7.72 ± 0.23	114	0.16	0.386	0.41	0.682
C. Antecubital Controls (1) vs. Toxemic Pregnancy, Ante Partum (2)								
All	7.88 ± 0.31	30	8.21 ± 0.39	72	0.33	0.498	0.66	0.509
D. Antecubital Normal Pregnancy (1) vs. Toxemic Pregnancy (2)								
25-28 wk. ap.	10.75 ± 1.66	4	9.33 ± 1.61	3	1.42	2.312	0.62	0.535
29-32	7.15 ± 0.76	10	8.11 ± 1.28	9	0.96	1.488	0.65	0.515
33-36	6.97 ± 0.39	19	9.44 ± 1.22	20	2.47	1.280	1.93	0.054 or 0.015(F)‡
37-38	7.11 ± 1.01	9	6.88 ± 0.50	9	0.23	1.127	0.20	0.841
39-40	7.64 ± 0.39	42	8.75 ± 0.82	24	1.11	0.908	1.22	0.223
1-2 days pp.	8.91 ± 0.69	16	12.39 ± 1.42	9	3.48	1.578	2.21	0.016 or 0.028(F)
3-20	7.70 ± 0.31	43	8.59 ± 0.89	17	0.89	0.942	0.95	0.347
5-40+ wk. ap.	7.72 ± 0.23	114	8.21 ± 0.39	72	0.49	0.452	1.09	0.275

*R or (k) = ratio of difference to its standard error.

†P = the probability of the (k) magnitude being exceeded solely through errors of random sampling.

‡P values followed by letter (F) are those computed by Fisher's small sample procedure.

E. Antecubital Normal Pregnancy, Ante Partum (1) vs. Same, Post Partum (2)								
All	7.72 ± 0.23	114	8.03 ± 0.29	59	0.31	0.370	0.84	0.401
39-40+ wk. ap. and 1-2 days pp.	7.64 ± 0.39	42	8.91 ± 0.69	16	1.27	0.972	1.30	0.194
F. Antecubital Normal Pregnancy, Post Partum (1) vs. Antecubital Controls (2)								
All	8.03 ± 0.29	59	7.88 ± 0.31	30	0.15	0.424	0.35	0.726
G. Antecubital Toxemias, 39-40+ Wks. (1) vs. Same, 1-2 days pp.								
All	8.75 ± 0.82	24	12.39 ± 1.42	9	3.64	1.640	2.22	0.026 or 0.016(F)
H. Femoral Controls (1) vs. Normal Pregnancy, Femoral (2)								
5-12 wk. ap.	11.43 ± 0.64	30	9.14 ± 1.45	7	2.29	1.584	1.45	0.147
13-16	11.43 ± 0.64	30	14.00 ± 3.14	7	2.57	3.207	0.80	0.424
17-20	11.43 ± 0.64	30	14.60 ± 1.89	5	3.17	1.995	1.59	0.112
21-24	11.43 ± 0.64	30	17.83 ± 0.88	15	6.40	1.087	5.89	0.000,000,002
25-28	11.43 ± 0.64	30	21.00 ± 1.15	6	9.57	1.315	7.28	Less than 0.000,000,002
29-32	11.43 ± 0.64	30	22.29 ± 0.83	12	10.86	1.047	10.37	Less than 0.000,000,002
33-36	11.43 ± 0.64	30	21.33 ± 0.80	27	9.90	1.024	9.67	Less than 0.000,000,002
37-38	11.43 ± 0.64	30	22.94 ± 0.94	18	11.51	1.135	10.14	Less than 0.000,000,002
39-40+	11.43 ± 0.64	30	24.37 ± 0.65	50	12.94	0.912	14.19	Less than 0.000,000,002
1-2 days pp.	11.43 ± 0.64	30	10.08 ± 0.36	26	1.35	0.734	1.84	0.066
3-4	11.43 ± 0.64	30	9.64 ± 0.58	21	1.79	0.864	2.07	0.038 or 0.140(F)
5-9	11.43 ± 0.64	30	9.04 ± 0.48	27	2.39	0.800	2.98	0.0029
10-20	11.43 ± 0.64	30	10.00 ± 1.73	6	1.43	1.844	0.78	0.435
I. Femoral Normal Pregnancy (1) vs. Femoral Toxemic Pregnancy (2)								
25-28 wk. ap.	21.00 ± 1.15	6	21.33 ± 2.53	3	0.33	2.778	0.12	0.905
29-32	22.29 ± 0.83	12	18.88 ± 1.16	8	3.41	1.425	2.39	0.017 or 0.018(F)
33-36	21.33 ± 0.80	27	20.86 ± 1.60	11	0.47	1.789	0.26	0.795
37-38	22.94 ± 0.94	18	23.07 ± 0.72	21	0.13	1.183	0.11	0.912
39-40+	24.37 ± 0.65	50	22.22 ± 0.95	27	2.15	1.150	1.87	0.062
1-2 days pp.	10.08 ± 0.36	26	13.05 ± 1.46	10	2.97	1.503	1.98	0.048
3-20	9.38 ± 0.35	54	9.22 ± 0.55	23	0.16	0.652	0.25	0.803
J. Post-Partum Femoral Normal Pregnancy (1) vs. Femoral Controls (2)								
All	9.61 ± 0.27	80	11.43 ± 0.64	30	1.82	0.695	2.62	0.0088
3-20 days pp.	9.38 ± 0.35	54	11.43 ± 0.64	30	2.05	0.729	2.81	0.0050

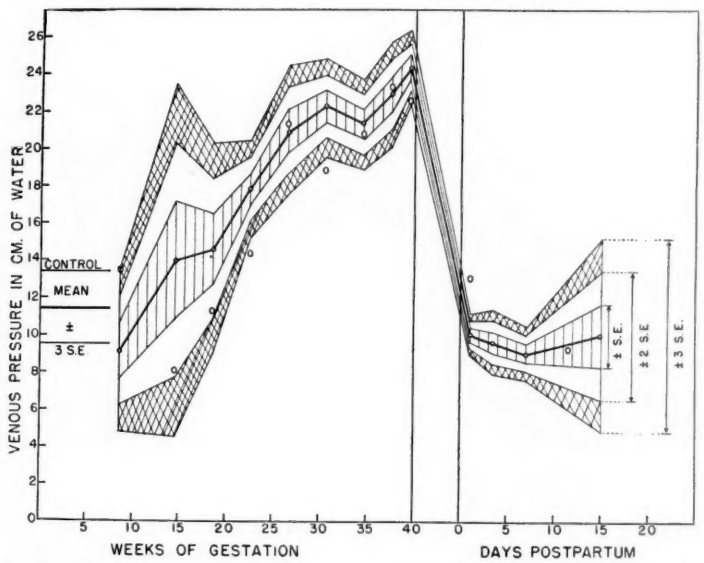

Fig. 2.—Showing the average course of femoral venous pressure throughout normal and toxemic pregnancy and the immediate puerperium. See legend of Fig. 1 for details.

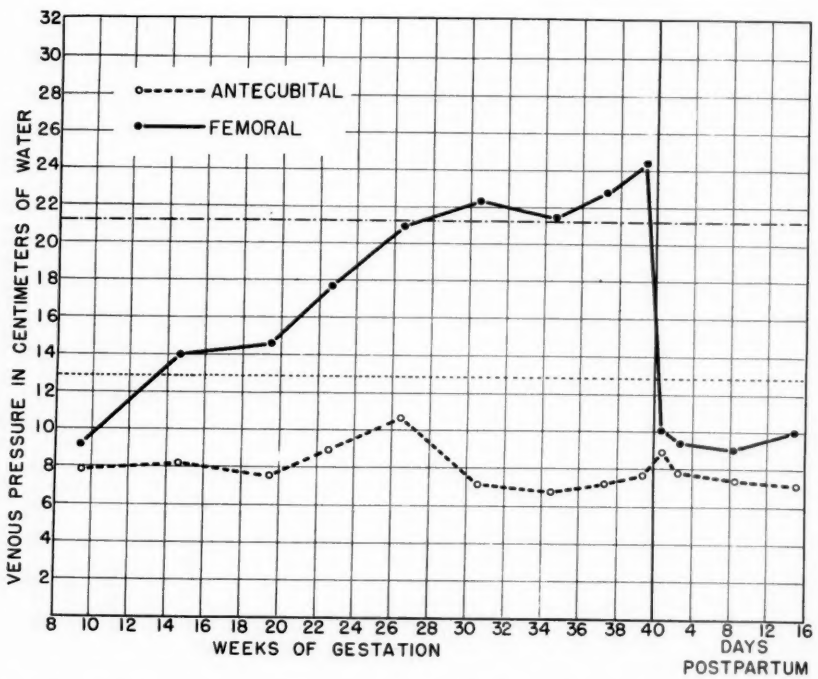

Fig. 3.—Showing the average course of antecubital and femoral venous pressure throughout normal pregnancy and the immediate puerperium, based on 173 antecubital and 227 femoral determinations in 160 pregnancies. The lower straight dotted line represents the upper limit of normal variation for antecubital venous pressure and the upper broken line the same for femoral venous pressure (i.e., control mean + 3 S. D.).

tested by the usual formulas or even by Fisher's small sample method (see Table II, D). When the mean of the ante-partum toxemia arm pressures is compared with that of the ante-partum arm pressures in the normally pregnant women the difference is not significant (Table II, D, last line), nor is it when the toxemia mean is compared with that of the nonpregnant controls (Table II, C). There is a difference of questionable significance between the toxemia arm pressure in the thirty-nine- to forty-week group and the one- to two-day post-partum group (Table II, G).

In Fig. 2 it may be observed that the mean values for femoral venous pressure fell within the normally pregnant range of means with the exception of the group for twenty-nine to thirty-two weeks and that for the first two days post partum. But in the latter instance the actual difference in means was not statistically significant and in the former it was only questionably so (Table II, I). While graphically (Fig. 2) the mean femoral pressure for toxemic women twenty-one to twenty-four weeks pregnant also falls just below the limit of normally pregnant mean minus three standard errors, little importance can be attached to this occurrence since the mean was derived from only two observations, one of which fell within the normally pregnant range and the other of which was somewhat below it.

4. *Changes in Femoral Venous Pressure During Parturition.*—Determinations of femoral venous pressure were made continuously, values being recorded every one-half, one, two, five, or ten minutes, during the performance of cesarean section. The course of the venous pressure in five such experiments is illustrated graphically in Figs. 4 and 5.

Detailed examination of the protocols for these experiments reveals that femoral venous pressure is exceedingly labile and fluctuates within a wide range during the course of an abdominal operation, particularly when the latter is performed under local anesthesia, as these were. While the use of local anesthesia is obviously advantageous for cesarean section operations, it added somewhat to the difficulties encountered in making continuous observations of venous pressure. In a number of experiments not reported here the results were invalidated by the fact that movements of the patients' lower extremities dislodged the needles from the venous lumina.

The momentary elevations of femoral venous pressure noted in Figs. 4 and 5 occurred for the most part during the early portions of the operations and appeared to be associated with such maternal factors as general muscular rigidity, holding of the breath, straining, talking, and crying. Certain manipulations on the part of the operator also produced transient rises in venous pressure, for example, palpating the exposed gravid uterus and attempting to rotate it within the abdominal cavity, retracting the abdominal walls to expose the uterine appendages, and exerting pressure over the site of the venipuncture (covered by sterile drapes) by inadvertently dropping a hand or instrument at that point. During the course of an oophorectomy in a patient twenty weeks pregnant (not illustrated), it was noted that the manipulations associated with delivery of a large tumor mass through the abdominal incision raised femoral venous pressure to more than 60 cm. of water from a previous level of about 22 cm.

In none of these operations was there any appreciable change in femoral venous pressure at the time the general peritoneal cavity was opened. This was true not only in the five experiments reported here,

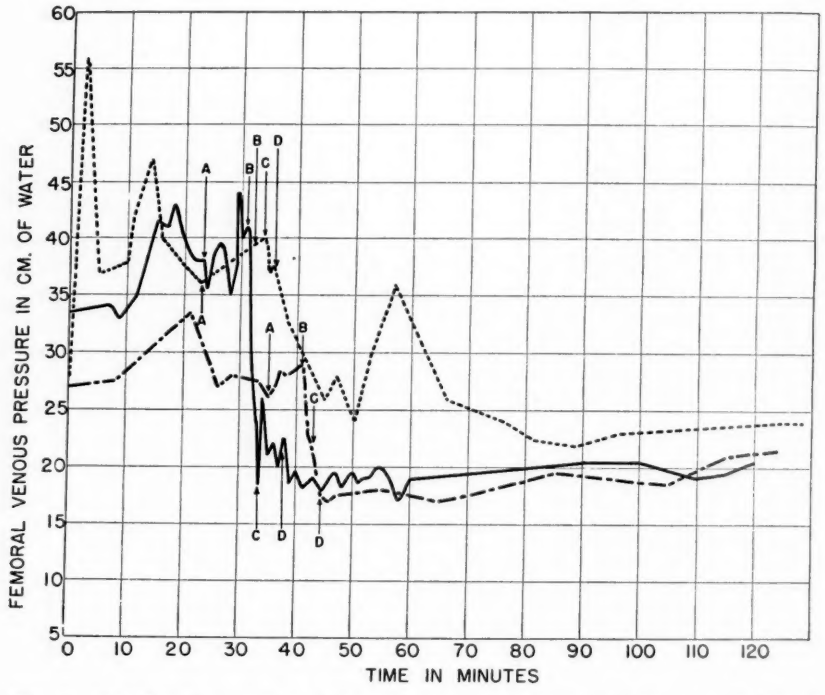

Fig. 4.—Showing the course of femoral venous pressure in 3 patients undergoing delivery by abdominal cesarean section. In each instance, at the point marked *A* the peritoneal cavity was opened, at *B* the uterine incision was started, at *C* the infant was delivered, and at *D* the placental extraction was completed. (See text for details.)

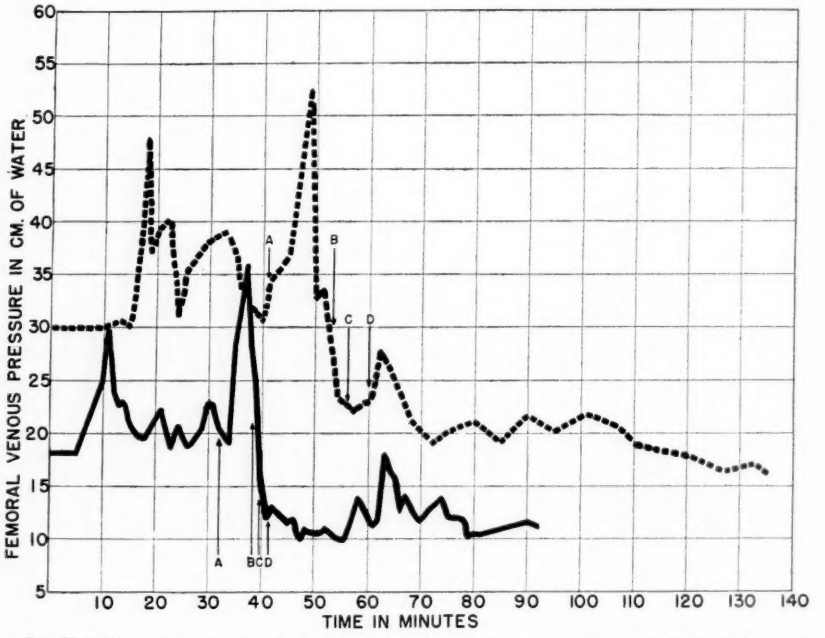

Fig. 5.—Showing the course of femoral venous pressure in two patients undergoing delivery by abdominal cesarean section. (See legend of Fig. 4 for details.)

but also in several others in which complete sets of determinations were not obtained because of disruptions in the manometer-vein communications later in the procedures. In the five complete cesarean section experiments the observed changes in femoral venous pressure associated with opening the uterus, rupturing the fetal membranes, extracting the infant, and extracting the placenta were quite variable. The only uniform observation was the lack of appreciable diminution in pressure at the moment of delivery of the placenta. It is difficult to say whether or not any major shift in pressure occurred at the time of placental separation from the uterine wall. In the first place, the precise moment at which separation occurred could not be determined, and second, the time between removal of the infant and delivery of the completely or partially separated placenta was so short that pressure changes attributable to extraction of the fetus undoubtedly masked any additional changes resulting from obliteration of the placental circulation. In the first observation (solid line, Fig. 4) it will be noted that a drop in pressure of 10.5 cm. occurred in the space of thirty seconds during the incision of the uterine wall and rupture of the fetal membranes; then an identical additional drop occurred during the removal of the infant, the manometer meniscus reaching a low point of 18.5 cm. of water at that time. A momentary rise of 7.5 cm. during the clamping of the cord may be attributed to the fact that the infant was resting to some extent on the mother's abdomen during this maneuver. When the child was removed the manometer reading fell again to 21.0 cm. of water and did not vary appreciably during the subsequent removal of the placenta. In the second experiment (lower broken line, Fig. 4) there was a more or less gradual drop in pressure over a period of five minutes from the time the uterine incision was begun until the umbilical cord was clamped, but the entire fall amounted to only 9.0 cm. of water. An additional drop of 1.5 cm. occurred with extraction of the placenta. A third observation (solid line, Fig. 5) showed a femoral pressure drop of 14 cm. of water during the opening of the uterus and delivery of the fetus, the major part of it appearing in connection with the latter process. Delivery of the placenta a minute later was not accompanied by any further diminution in pressure. In the fourth case (dotted line, Fig. 5), there was a drop in pressure of only 4.5 to 5 cm. in the four minutes required for incising the uterus and removing the infant, no further drop with delivery of the placenta, but an additional slow decrease of 5 to 6 cm. during the ensuing seventy-five minutes under general anesthesia. And the fifth case (upper dotted line, Fig. 4) exhibited no appreciable pressure change with removal of either fetus or placenta, although subsequently it fell gradually to a point considerably below the existing level just prior to delivery of the infant. In this particular operation the femoral venous pressure at the end of the procedure was only 4 cm. lower than it had been in the resting state at the beginning of the operation, while in the other four cesarean section observations the differences between initial and final pressure readings were, respectively, 13, 5, 7, and 14 cm. of water.

5. *Venous Pressure in the Presence of Gynecologic Tumors.*—In twelve gynecologic patients with uterine, ovarian, parovarian, and tubal tumors of varying size, both antecubital and femoral venous pressure determinations were made preoperatively and postoperatively. Inspection of the individual values (Table III) for venous pressure reveals that in all instances preoperatively the femoral pressure was higher

than the antecubital and that with one exception the antecubital pressures were within the normal range. Furthermore, all but one of the initial femoral readings may be said to be "elevated" on the basis of the fact that they lie above the range of the control mean ± 3 S. E., i.e., 9.52 to 13.34 cm. of water; and likewise they are above the range of the mean value for 80 determinations in normal post-partum individuals, 8.80 to 10.42 cm. of water. However, if one wishes to judge the normalcy of a single determination by whether or not it falls within the range of control mean + 3 standard deviations, then only five of the femoral pressure readings in these tumor patients fall above the possible limit for controls (21.73 cm. of water), whereas eight of them fall above the same limit for the normal post-partum values (16.73 cm. of water).

It is difficult, of course, to compare these findings directly with the results of venous pressure measurements in pregnant subjects because

TABLE III. ANTECUBITAL AND FEMORAL VENOUS PRESSURES BEFORE AND AFTER OPERATION IN PATIENTS WITH GYNECOLOGIC TUMORS

CASE	AGE YEARS	PRE-OPERATIVE DAY	POST-OPERATIVE DAY	ANTECUBITAL VENOUS PRESSURE CM. WATER	FEMORAL VENOUS PRESSURE CM. WATER	TYPE AND SIZE OF TUMOR
1	48	1		8.5	18.0	Fibroma ovarii 15 x 12 x 10 cm.
			13	7.5	10.5	
2	71	4		4.5	8.5	Pseudomucinous cystadenoma ovarii 26 x 22 x 17 cm.
			10	3.5	4.0	
3	44	360		9.5	20.0	Myoma uteri 12 x 11 x 9 cm.
4	48	3		3.0	23.5	Myomata uteri 22 x 22 x 16 cm.
			9	11.0	9.0	
5	29	5		7.5	11.5	Myomata uteri 12 x 10 x 9 cm.
			11	5.5	5.0	
6	29	1		7.5	17.0	Serous cystoma ovarii and pregnancy, 16 weeks. Cyst 32 x 24 x 12 cm.
			1	7.5	13.5	
			10	3.0	10.5	
7	29	2		5.0	25.0	Parovarian cyst 25 x 20 x 11 cm.
			11	6.5	7.5	
8	50	–		25.5	29.5	Adenocarcinoma corpus uteri; marked obesity
9	20	1		12.0	26.5	Pseudomucinous cystadenoma ovarii and pregnancy, 22 weeks. Cyst 20 x 14 x 10 cm.
			12	10.0	19.0	
10	68	2		9.5	15.5	Carcinoma 1. Fallopian tube 13 x 10 x 9 cm.
11	52	1		8.5	15.0	Serous cystadenoma ovarii, 20 x 17 x 15 cm.
			10	8.5	9.5	
12	44	1		12.0	31.0	Pseudomucinous cystadenoma ovarii 27 x 24 x 20 cm.
			9	10.0	13.0	

of differences in size and shape in the tumor masses, as well as differences in weight and location. But in general, it may be said that many of these gynecologic tumors were associated with elevations of femoral venous pressure entirely comparable in magnitude to those seen in the latter months of pregnancy. The sizes of the various tumors which were removed surgically are noted in Table III as three-dimensional measurements in centimeters. From these figures it may be seen that the largest masses were not always found in the persons with the highest venous pressure levels in the lower extremities. In Case 2, for example, a very large pseudomucinous cystadenoma of the right ovary in a thin elderly woman was associated with a femoral venous pressure of only 8.5 cm. of water, while in Case 8 a moderate enlargement of the uterus carried with it a rather tremendous elevation of femoral venous pressure. But the latter apparently cannot be attributed to the uterine mass, since the antecubital venous pressure in this instance also was much above normal levels despite complete lack of other evidences of cardiac decompensation. It is possible that the extreme obesity of the patient was a factor in the disturbance of venous pressure. Finally, it may be pointed out that an appreciable lowering of femoral venous pressure occurred in all of these individuals after removal of the tumors.

6. *The Effect of Intrauterine Fetal Death on Venous Pressure in the Lower Extremities.*—In eight subjects determinations of both antecubital and femoral venous pressure were made after intrauterine death of the fetus. In most instances, of course, it was impossible to determine with any degree of accuracy the exact date of fetal death, so that difficulties arose in attempting to define the duration of gestation in the various cases. Table IV gives the venous pressures, fetal weights, aver-

TABLE IV. ANTECUBITAL AND FEMORAL VENOUS PRESSURES IN PREGNANT WOMEN WITH DEAD FETUSES

CASE	WEEKS PREGNANT BY HISTORY	PROBABLE DURATION ON BASIS OF FETAL WEIGHT WEEKS	ANTECUBITAL VENOUS PRESSURE CM. WATER	FEMORAL VENOUS PRESSURE CM. WATER	FETAL BIRTH WEIGHT GRAMS	AVERAGE EXPECTED BIRTH WEIGHT BY HISTORY* GRAMS
1	18	17	8.0	9.5	180	198
2	20	21	12.0	18.0	350	316
3	28	28½	8.0	21.0	1,090	1,045
4	29	28	7.0	21.0	1,070	1,174
5	30	27	13.0	13.5	870	1,323
6	37	33½	6.0	20.5	1,920	2,690
7	39	35½	11.0	11.5	2,370	3,150
8	40	40+	5.0	17.5	3,605	3,405

*Data computed by A. L. Dippel from figures of G. L. Streeter, Contributions to Embryology, vol. XI, Carnegie Institution of Washington, Pub. No. 274, 1920, Table I.

age expected fetal weights for the apparent menstrual ages, and probable durations of fetal lives on the basis of known birth weights. Only three of the femoral venous pressure values fall below the normally pregnant mean pressure minus 3 S. E. as illustrated in Fig. 2, namely, those for Cases 5, 7, and 8. The pressures in Cases 5 and 7 also are beyond the range of normally pregnant mean ± 2 standard deviations (accounting for more than 95 per cent of the variability), but this is not true of the value for Case 8 (which is 17.5 cm. of water, while the normal mean value at term, less twice its standard deviation, is 15.2

cm.). When the femoral pressure readings for Cases 5 and 7 are compared with normally pregnant means for the probable fetal age rather than the age by menstrual history they still are lower than the limits of normal mean ± 2 S. E.

Discussion

The average values for venous pressure obtained in the normal control subjects fall well within the range of "normal" previously reported. The determinations on this group of 30 nonpregnant women were made not so much with the purpose of once again defining normal limits of venous pressure as with a view to demonstrating the adequacy of the particular method employed in this study. It should be noted that, while on the average venous pressure was about 3.5 cm. higher in the femoral than in the antecubital vein, this leg-arm relationship was not invariable in individual instances. If the pressure gradient in the venous system which Burton-Opitz[26, 27] described in the dog exists in the human being, then one might expect that pressure in the femoral vein always would be somewhat above that in an arm vein of the same subject. In fact, McIntire and Turner[28] concluded that venous pressure in foot veins of a supine subject invariably was higher than that in the hand veins, since the foot was farther from the heart and thus a higher pressure was required to maintain the gradient of circulation. While this concept was borne out by the statistically significant difference between femoral and antecubital mean values in the present control series, it would appear that certain uncontrollable or perhaps technical factors occasionally enter into the determinations in individual cases so that the expected relationship sometimes is disturbed.

Although Thomson, Reid and Cohen,[18] as well as Landt and Benjamin,[14] have suggested that venous pressure in the arm is higher in the early months of pregnancy than in the latter months, such a trend is not confirmed by this study, unless one chooses to say, for example, that a mean value of 7.72 cm. of water (at term) is significantly lower than 7.85 or even 8.07 cm. of water (means for five to twelve and thirteen to sixteen weeks). In any event, it may be definitely stated that arm venous pressure in normal pregnancy, despite its minor fluctuations, is at all times well within the normal limits for nonpregnant persons. Statements to the contrary in the literature would seem to be based upon inaccurate and insufficient numbers of observations as well as untenable concepts of the upper limits for normal values.

The observations of femoral venous pressure in normal pregnancy substantiate the statements of previous investigators, notably Runge[4] and Burwell, Strayhorn and others.[3] There would seem to be no doubt that venous pressure in the lower extremities begins to rise above its usual levels by the beginning of the second trimester and continues to increase throughout the remainder of pregnancy, the rate of increase being most marked between the twentieth and thirtieth weeks of gestation. The upward progression of pressure is not constant in all indi-

viduals on bed rest; many of these show minor decreases in femoral venous pressure after some days or weeks in bed, despite advancing pregnancy, but average figures demonstrate a continuous upward trend. It is likely that the apparent slight drop in the mean value between thirty-three and thirty-six weeks may be explained on the basis of the relatively small number of observations in the preceding group, tending to make its mean somewhat too high. It should be noted, however, that while the mean femoral vein pressure in the last two weeks of pregnancy was more than double that of the nonpregnant control subjects, it was less than 3 cm. above the limit of control mean plus three standard deviations. In other words, although individual rises in femoral venous pressure are striking and unmistakable, and although the mean values early and late in pregnancy are clearly far apart, still the average value at term cannot be looked upon as enormously elevated by comparison with the possible range of normal variation in this measurement.

Granted that there is a real elevation of venous pressure below the level of the pregnant uterus, two questions present themselves for argument. First, what is the reason for the abnormal pressure, and second, is the pressure of sufficient magnitude to cause disturbances in the normal circulatory mechanism? Burwell and his co-workers[1-3] have pointed out that the pressure exerted by the blood in any vein is dependent partly on the resistance to its outflow and partly on the amount and the pressure of the blood flowing in. They admit that their observations of venous pressure in patients with pelvic tumors strongly suggest that an important factor in the rise of venous pressure is interference with venous flow by the pressure of the enlarging uterus. But at the same time they apparently feel that the factor of increased flow into the veins draining the uterus (Runge) may be equally operative in producing elevations of venous pressure. Their evidence in favor of the latter concept is two-fold: (1) observations in pregnant bitches showing that femoral venous pressure fell when the gravid uterus was lifted from the abdomen so that it no longer pressed upon the great veins, but that even then the pressure usually remained above the pressure in the jugular vein; (2) Spanner's[29] anatomic description of the vascular system of the placenta, indicating that arteries connect with veins through large vascular spaces and without the interposition of arterioles or capillaries, a structure, then, similar in many respects to a simple arteriovenous shunt. It should be mentioned here that Stieve[30] has taken exception to that portion of Spanner's work dealing with the return venous flow from the placenta, although there is no evidence that the description of the manner in which terminal arteries empty into intervillous spaces is incorrect.

While the arteriovenous shunt circulatory changes may quite adequately explain the vast majority of the phenomena observed during pregnancy, there is as yet no adequate explanation for the apparent

lack of rise in arterial blood pressure at the time of occlusion of the shunt-like circulatory mechanism in the placenta. In view of the blood pressure changes observed after closure of arteriovenous fistulas (Reid and McGuire[31]), one might expect such a finding post partum in at least some instances.

Despite the general attractiveness of Burwell's arteriovenous shunt explanation for the alterations in the circulation of pregnant women, the present investigation does not support the notion that the rise in venous pressure of the lower extremities is to any great extent the result of the peculiar placental circulation. In the first place, elevations of femoral venous pressure entirely comparable with those in pregnancy are seen in association with gynecologic tumors. Second, the observations made during cesarean sections, although by no means conclusive, certainly would indicate that the presence of the fetal mass in utero was the major factor in maintaining venous pressure at abnormal levels. Third, observations on patients with dead fetuses in utero suggest that cessation of the placental circulation may not be followed by a demonstrable diminution in venous pressure in the femoral vein. This latter evidence is, of course, open to serious question since one cannot be certain that fetal death necessarily implies occlusion of the intervillous circulation.

Regardless of the precise cause of the elevation in venous pressure, some consideration must be given to the possible effects of such a disturbance. Is the rise in femoral venous pressure late in pregnancy of sufficient magnitude to change capillary pressure and influence the movement of fluid through the capillary walls in a manner conforming to the Starling[32] hypothesis? In the light of the observations of Krogh, Landis and Turner,[33] as well as those of Landis and Gibbon,[34] one must conclude that a venous pressure of 24 cm. of water (mean femoral venous pressure at term) is sufficient to filter fluid into the tissues. Krogh and others,[33] for example, noted that the rate of filtration was directly proportional to the increase in venous pressure above an average venous pressure of 17 cm. of water, while Landis and Gibbon[34] found this to be true above an average pressure of 12 cm. of water. However, at venous pressures in the neighborhood of 20 to 25 cm. of water the actual quantity of fluid filtered per minute is not particularly great, and it seems unlikely that this increase in filtration would overburden the mechanisms for the removal of tissue fluid. Furthermore, in the presence of continued venous congestion, some force, presumably tissue pressure, diminishes the power of a given venous pressure to filter fluid from the blood into the tissue spaces. For example, in the experiments of Landis and Gibbon,[34] when the filtered fluid amounted to 1.0 c.c. per 100 c.c. of arm, filtration was decreased approximately 0.033 c.c. per minute per 100 c.c. of arm, a change which corresponded to the effect of lowering venous pressure by 10 cm. of water. The accumulation of 1.5 c.c. of fluid per 100 c.c. of tissue resulted in the rapid

removal of fluid even with a venous pressure of 20 cm. of water. Additional evidence that venous pressures of 20 to 25 cm. of water are not particularly effective filtering pressures is brought out in the study of Landis, Jonas, Angevine and Erb,[35] where filtration was measured indirectly by determining cell volume, hemoglobin and erythrocyte counts. While loss of fluid from the blood was conspicuous at venous pressures of 40 to 80 mm. of Hg, it could barely be detected at a venous pressure of 20 mm. Hg (27 cm. of water).

Available data from direct measurements seem to show that tissue pressure is not always significantly elevated by prolonged venous congestion and that even in edema the values are not nearly as high as would be expected (Burch and Sodeman[36]). But it should be remembered that these data refer only to subcutaneous and intracutaneous pressures. Wells, Youmans and Miller,[37] on the other hand, have measured tissue pressure in muscle as well as in the superficial tissues; their interest centered mainly on the leg because of the well-known paradox of the failure of edema to develop in legs of normal individuals on prolonged quiet standing. It would appear that in the tightly covered muscles, as the soleus and anterior tibial, tissue pressure starts at a high level and increases quite rapidly to values which are of the magnitude required by Starling's hypothesis to oppose effectively further filtration (50 cm. of water, or higher, in some experiments). In more loosely covered muscles, such as the gastrocnemius, intramuscular pressure remains at lower levels which probably are ineffective in stopping filtration; the same seems to be true for the skin. Because of this latter relationship, the leg volume may continue to increase during quiet standing at a low residual rate (maximum time of observation was 2.5 hours). These workers feel that it is not necessary to postulate extensive lymphatic drainage from the congested area to account for the retardation in the rate of swelling of the leg, as suggested by Beecher.[38]

The experiments of Drury and Jones[39] demonstrated that palpable edema in the leg did not occur until the amount of collected tissue fluid had increased the limb volume by 8 per cent. If this be true, then, in the light of what has just been said about filtration rates at low venous pressures, it seems quite unlikely that the venous pressure existing in the femoral vein in the latter part of pregnancy could lead routinely to the production of clinical, pitting edema. And this is borne out, of course, by the fact that while all pregnant women at term exhibit elevated femoral venous pressure, not all have pitting edema of the lower extremities. On the other hand, it must be concluded that the increased venous pressure in pregnancy does tend to promote the accumulation of tissue fluid in the lower extremities, and thus set up subclinical degrees of edema which are easily and quickly thrown over into detectable edematous states by some further derangement of the normal mechanism for fluid exchange. It should be remembered in

this regard that edema appearing in warm weather is undoubtedly in part due to the accelerated accumulation of tissue fluid because of the increase in temperature of the part involved. This effect of temperature on rates of filtration was clearly shown in the experiments of Landis and Gibbon, where, for example, the rate of filtration at 44° C. was twice as great as that at 14° C.

The recent work of Linton and others[40] on the effect of venous occlusion on arterial inflow to an extremity raises the question of whether blood flow in the lower extremities of pregnant women may be appreciably increased because of venous congestion. The congestion in pregnancy, of course, is not intermittent, as it is when employed therapeutically. Abramson, Flachs and Fierst,[41] however, have reported that they could demonstrate no significant change from the normal in blood flow in the legs of pregnant women, although some of their subjects seem to show a trend toward an increased flow during the last lunar month of gestation.

The data for the toxemia patients in the present study refute statements in the literature to the effect that antecubital venous pressure is elevated in toxemia of pregnancy. As has already been pointed out by Thomson, Reid and Cohen,[18] the level of the venous pressure in toxemia in no way correlates with the severity of the disease, the degree of edema or the height of the arterial blood pressure. This result one might have anticipated in view of the many previous reports on the absence of correlation between arterial and venous blood pressures.[17, 42-44]

The statistically significant difference between the mean femoral venous pressure post partum and the mean for the normal control subjects requires some comment. At least two possible explanations for this observation have suggested themselves. The first is that these subjects were on continuous and absolute bed rest. It is conceivable that prolonged assumption of the supine posture tends to bring the femoral venous pressure to a level somewhat below the average for persons who have only a few minutes previously abandoned the upright position, with its known increments in venous pressure in the lower extremities. Second, certain observations not reported here point to the fact that the slight sagging of the bed at the site of the buttocks may be a factor in depressing venous pressure 2 to 3 cm. of water in the femoral vein. On theoretical grounds, it would seem that a lowering of this part of the body would tend to raise femoral venous pressure when the manometer is kept at the same level as that used for the arm determination. However, it was repeatedly observed that femoral venous pressure in subjects lying on a firm, perfectly horizontal examining table was somewhat higher than that in persons lying in bed. In an attempt to discover the effect of lowering the general region of the buttocks, subjects were placed on a delivery table with a depressable foot section. Supporting the feet and legs distal to the table, and the head and chest on the stationary portion, it was possible to lower the pelvic region below the

general level of the rest of the body. When this was done, with continuous observation of femoral venous pressure, it was found that the femoral pressure invariably fell as the buttocks were depressed and rose again to the initial level when the buttocks were restored to their original position. I have no adequate explanation for this apparently paradoxical phenomenon. When the entire body was tilted to a semierect posture, the expected change (Mayerson and Burch[45]) in femoral pressure occurred, that is, a marked rise, and conversely, in the Trendelenburg position, femoral venous pressure dropped to very low levels.

Summary and Conclusions

By a direct method, 757 determinations of venous pressure were made in 255 subjects. Three hundred and forty-five determinations were made in the antecubital vein and 412 in the femoral vein. The subjects were normal nonpregnant females, normally pregnant women, normal postpartum patients, pregnant women with hypertensive toxemias, and gynecologic patients with pelvic tumors. In some instances determinations were made during the course of operative delivery by abdominal cesarean section. Accepted statistical formulas were employed in the analysis of the results.

In 30 normal, nonpregnant women the average antecubital venous pressure in the supine posture was 7.88 ± 0.31 cm. of water and the average femoral venous pressure was 11.43 ± 0.64 cm. of water.

Antecubital venous pressure in normal pregnancy is not significantly different from that in the nonpregnant state and shows no particular trends during the course of pregnancy. Femoral venous pressure in normal pregnancy begins to rise in the early part of the second trimester, rises rather rapidly between the twentieth and thirtieth weeks of gestation, then somewhat more slowly to reach an average peak value at term of approximately 24 cm. of water. It falls quickly after delivery to nonpregnant levels and apparently lies somewhat below the average control level during the puerperal period of bed rest.

Patients with toxemia of pregnancy have antecubital and femoral venous pressures within the range of those for normally pregnant persons.

During the course of abdominal cesarean section, femoral venous pressure usually shows a marked decline after removal of the fetus from the uterine cavity, and is not appreciably affected by opening the peritoneal cavity, incising the uterine wall, or delivery of the placenta. Because of the short time interval between delivery of the fetus and of the placenta, such observations have not been of great value in differentiating between that increment of venous pressure resulting from the presence of the fetal mass and enlarged uterus and that owing possibly to a transfer of high arterial pressures at the placental site (arteriovenous shunt effect).

Patients with large pelvic tumors exhibit elevations of femoral venous pressure entirely comparable to those seen late in pregnancy. These pressures return to normal values after removal of the tumor masses.

Pregnant women with dead fetuses in utero appear, for the most part, to have elevations of femoral venous pressure of a magnitude similar to those seen in normal pregnancies with living fetuses.

Reasons are presented for thinking that the level of venous pressure observed in the lower extremities, while admittedly abnormal, is not sufficiently high to produce obvious pitting edema in all pregnant women, although it probably promotes subclinical degrees of edema routinely.

The present study does not suggest that the elevation of femoral venous pressure in pregnancy is to any great extent the result of an arteriovenous-shuntlike mechanism operating in the placenta. The abnormal venous pressure appears to be the result of obstruction to venous return by the pregnant uterus.

References

1. Burwell, C. S.: Ann. Int. Med. **11:** 1305, 1938.
2. Burwell, C. S.: Am. J. M. Sc. **195:** 1, 1938.
3. Burwell, C. S., Strayhorn, W. D., Flickinger, D., Corlette, M. B., Bowerman, E. P., and Kennedy, J. A.: Arch. Int. Med. **62:** 979, 1938.
4. Runge, H.: Arch. f. Gynäk. **122:** 142, 1924.
5. Fuchs, L.: Deutsches Arch. f. klin. Med. **135:** 68, 1921.
6. Moritz, F., and von Tabora, D.: Deutsches Arch. f. klin. Med. **98:** 475, 1910.
7. Kaboth, G.: Arch. f. Gynäk. **127:** 170, 1925.
8. Villaret, M., Saint-Girons, Fr., and Salasc, L.: Ann. de. Med. **18:** 87, 1925 (abstr. in Compt. rend. Soc. de biol. **93:** 230, 1925).
9. Dellepiane, G.: Riv. ital. di ginec. **6:** 145, 1927 (abstr. in Ber. ü. d. ges. Gynäk. u. Geburtsh. **13:** 126, 1928).
10. Krukenberg, H.: Ztschr. f. Geburtsh. u. Gynäk. **103:** 217, 1932.
11. Baráth, E., and Weiner, P.: Ztschr. f. klin. Med. **125:** 243, 1933.
12. Strauss, M. B.: Am. J. M. Sc. **190:** 811, 1935.
13. Róna, A.: Ztschr. f. Geburtsh. u. Gynäk. **112:** 62, 1935.
14. Landt, H., and Benjamin, J. E.: Am. Heart J. **12:** 592, 1936.
15. Cohen, M. E., and Thomson, K. J.: J. Clin. Investigation **15:** 607, 1936.
16. Luisi, M.: Riv. ital. di ginec. **21:** 1, 1938.
17. Thomson, K. J., Hirsheimer, A., Gibson, J. F., 2nd, and Evans, W. A., Jr.: Am. J. Obst. & Gynec. **36:** 48, 1938.
18. Thomson, K. J., Reid, D. E., and Cohen, M. E.: Am. J. M. Sc. **198:** 665, 1939.
19. Veal, J. R., and Hussey, H. H.: Surg., Gynec. & Obst. **72:** 841, 1941.
20. Hamilton, B. E., and Thomson, K. J.: The Heart in Pregnancy and the Childbearing Age, Boston, 1941, Little, Brown and Company.
21. Dexter, L., and Weiss, S.: Preeclamptic and Eclamptic Toxemia of Pregnancy, Boston, 1941, Little, Brown and Company.
22. Lyons, R. H., Kennedy, J. A., and Burwell, C. S.: Am. Heart J. **16:** 675, 1938.
23. Ferris, E. B., Jr., and Wilkins, R. W.: Am. Heart J. **13:** 431, 1937.
24. Treloar, A. E.: Elements of Statistical Reasoning, New York, 1939, John Wiley and Sons, Inc.
25. Fisher, R. A.: Statistical Methods for Research Workers, ed. 6, Edinburgh and London, 1936, Oliver and Boyd.
26. Burton-Opitz, R.: Am. J. Physiol. **9:** 161, 1903.
27. Burton-Opitz, R.: Am. J. Physiol. **9:** 198, 1903.
28. McIntire, J. M., and Turner, A. H.: J. Clin. Investigation **14:** 16, 1935.
29. Spanner, R.: Ztschr. f. Anat. u. Entwicklungsgesch. **105:** 163, 1936.
30. Stieve, H.: Zentralbl. f. Gynäk. **64:** 1570, 1940.
31. Reid, M. R., and McGuire, J.: Ann. Surg. **108:** 643, 1938.
32. Starling, E. H.: J. Physiol. **19:** 312, 1896.
33. Krogh, A., Landis, E. M., and Turner, A. H.: J. Clin. Investigation **11:** 63, 1932.

34. Landis, E. M., and Gibbon, J. H., Jr.: J. Clin. Investigation **12**: 105, 1933.
35. Landis, E. M., Jonas, L., Angevine, M., and Erb, W.: J. Clin. Investigation **11**: 717, 1932.
36. Burch, G. E., and Sodeman, W. A.: J. Clin. Investigation **16**: 845, 1937.
37. Wells, H. S., Youmans, J. B., and Miller, D. G., Jr.: J. Clin. Investigation **17**: 489, 1938.
38. Beecher, H. K.: J. Clin. Investigation **16**: 733, 1937.
39. Drury, A. N., and Jones, N. W.: Heart **14**: 55, 1927.
40. Linton, R. R., Morrison, P. J., Ulfelder, H., and Libby, A. L.: Am. Heart J. **21**: 721, 1941.
41. Abramson, D. I., Flachs, K., and Fierst, S. M.: Proc. Fed. Am. Soc. Exper. Biol. **1**: 1, 1942.
42. Arnoldi, W.: Deutsche med. Wchnschr. **46**: 4, 1920.
43. Criep, L. H.: Med. Bull. Vet. Admin. **8**: 463, 1932.
44. Krinsky, C. M., and Gottlieb, J. S.: Arch. Neurol. & Psychiat. **35**: 304, 1936.
45. Mayerson, H. S., and Burch, G. E.: Am. J. Physiol. **128**: 258, 1940.

HYPERTHYROIDISM COMPLICATING PREGNANCY

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THE problems presented by hyperthyroidism complicating pregnancy have been of great interest to surgeons and obstetricians alike during recent years. During the ten-year period from 1932 to 1942 a total of 6,112 obstetric patients were delivered in the University Hospital or on the out-call service under the supervision of the obstetric staff. Thyrotoxicosis was observed as a complication of pregnancy in 19 women, an incidence of 0.3 per cent. An analysis of these 19 patients was undertaken, together with a review of the experience of others, in an effort to determine the most satisfactory method of treatment.

The incidence of thyrotoxicosis complicating pregnancy varies markedly in different sections of this country and in various parts of the world. In general those sections in which goiter is endemic will see many more cases than those in which thyroid disease is less commonly encountered. In Table I is listed the occurrence of hyperthyroidism and pregnancy as observed in several sections of America. From this it may be assumed that hyperthyroidism will be present or develop in approximately 0.22 per cent of all women during pregnancy. It is interesting to note that the incidence of pregnancy in established thyroid disease is over three times as high as the incidence of thyroid disease developing during pregnancy. In England Gardiner-Hill has reported a series of 115 women with hyperthyroidism during pregnancy, of whom 89 were classified as typical Graves' disease. He concluded that pregnancy occurred in about 50 per cent of those patients with primary exophthalmic goiter in which it was possible but noted that more than one

TABLE I. THYROTOXICOSIS AND PREGNANCY (INCIDENCE IN REPORTED SERIES)

AUTHOR	YEAR	REGION	SERIES OF PREGNANCIES	CASES HYPERTHYROIDISM IN PREGNANCY	PERCENTAGE INCIDENCE
Yoakam	1928	Michigan	937	35	3.7
Wallace	1933	New York	11,571	9	0.07
Portis and Roth	1939	Illinois	1,000	14	1.4
Javert	1940	New York	23,439	18	0.076
McLaughlin and McGoogan	1942	Nebraska	6,112	19	0.3
Total			43,059	95	0.22
AUTHOR	YEAR	REGION	SERIES OF THYROIDECTOMIES	NO. PATIENTS PREGNANT	PERCENTAGE INCIDENCE
Mussey	1926	Minnesota	7,228	42	0.5
Clute and Daniels	1929	Massachusetts	3,678	18	0.41
Frazier and Ulrick	1932	Pennsylvania	1,350	38	3.2
Bram	1936	Pennsylvania	4,000	12	0.3
Total			15,256	110	0.72

pregnancy after the onset of the disease was rare. Bram studied the menstrual histories of 4,000 patients with Graves' disease, finding it normal in 31 per cent, delayed or irregular in 43 per cent, amenorrhea present in 24 per cent, and menorrhagia in 2 per cent.

In normal pregnancy there occurs a very definite alteration in the function and balance of the ductless gland system and this is further affected by the development of hyperthyroidism.

The normal variations in the basal metabolic rate during and immediately following pregnancy have been rather extensively studied by a number of investigators (Sandiford and Wheeler, Hanna, Cornell, Enright, Cole, and Hitchcock, Root and Root, and Hughes). All of these observers are essentially in agreement that the basal metabolic rate remains normal during the first four or five lunar months of pregnancy, gradually rising during the last three or four months to reach an average increase of 20 to 25 per cent above the normal at term. Following delivery the basal metabolic rate promptly falls within ten days to a normal level but is usually a little below the readings obtained during the fourth and fifth lunar months of pregnancy. This elevation in the basal metabolic rate is resultant from the presence of an increasing mass of protoplasmic or fetal tissue, to a lesser extent an increase in maternal structure, and to simple hypertrophy and hyperplasia of the thyroid gland. It tends to be much more apparent in young girls than in mature women. Plass and Yoakam have observed that women with palpable thyroid glands show a greater tendency to high basal metabolic rates during pregnancy. Those with small colloid or adenomatous glands developed an average increase of 35 per cent in their basal metabolic rate, while those with larger colloid goiters had an elevation of approximately 50 per cent. Yoakam, Hinton, and Hanna have each observed enlargement of the thyroid gland in approximately 50 per cent of pregnant women under observation confirming the presence of an increased thyroid mass during these months, particularly noticeable in the thyroid belts.

In experimental studies with guinea pigs, Hewitt and Van Liere were unable to demonstrate any true increase in the thyroid weight: body weight ratio during pregnancy; either early, late, or during the postpartum period. Soule demonstrated experimentally a substance in the blood serum of pregnant women capable of reducing the liver glycogen level in the mouse with a resultant increase in the level of circulating thyroid hormone. He concluded that an actual physiologic hyperfunction of the thyroid gland during pregnancy was responsible for the increase in the thyroid hormone.

These findings make it extremely important that the clinician differentiate between thyroid hyperplasia and true thyrotoxicosis during pregnancy.

Enright, Cole, and Hitchcock have shown that the administration of iodized salt during pregnancy furnishes an adequate amount of iodine and prohibits in part the usual elevation in the basal metabolic rate during the third trimester. Phatak, Zener, and David have confirmed these observations, pointing out that the supplemental iodine is utilized principally during the third trimester of pregnancy when the blood iodine level tends to decrease in those patients from whom iodine medication is withheld. Hughes[18] reports two patients with signs of hyperthyroidism developing during the third trimester of pregnancy. Both had thyroidectomies following delivery and in neither case was the tissue pathologically as active as anticipated. He suggests that the presence of true hyperthyroidism can best be judged and evaluated during the first trimester of pregnancy when thyroid activity is usually within normal limits. In one of our patients (Case 14) subjected to thyroidectomy during the third month of pregnancy, the excised tissue showed only thyroiditis with no evidence of activity, casting some question on the preoperative diagnosis of exophthalmic goiter.

Clute and Daniels in an extensive experience with thyroid disease state that pregnancy does not appear to be a cause of primary hyperthyroidism and conclude that "we have never seen anything occur in any woman with hyperthyroidism and pregnancy which does not commonly occur in nonpregnant thyroid cases of that type."

There is good evidence that the toxemias of pregnancy occur more frequently in those cases complicated by thyroid disease.

Javert observed some degree of toxemia in 76 per cent of his 18 cases of associated hyperthyroidism and pregnancy in contrast to an incidence of 7.6 per cent in noncomplicated cases, raising the question of a common etiology. Colvin and Bartholomew noted the frequent occurrence of toxemia in young primiparas with normal or subnormal basal rates and a high blood cholesterol during the first trimester of pregnancy. With the development of a true toxemia, the basal metabolic rate promptly rises with an associated fall in the blood cholesterol; both figures returning to normal amounts during the puerperium. These authors advise the administration of thyroid extract with a restriction of cholesterol-containing foods to prevent the late toxemias of pregnancy. Hughes[19] reports that the administration of thyroid to patients with low basal

rates during the first trimester of pregnancy has reduced the incidence of late toxemias by 50 per cent, but warns that medication must be given early in pregnancy.

There is no unanimity of opinion in the literature on the effect of hyperthyroidism upon the unborn child, excepting an occasional reference to fetal abnormalities. Dean reports a mother with simple goiter who in succession was delivered of two anencephalic monsters, each with enlarged thyroids. Subsequently when placed on iodine a normal male child was delivered. Warren and Shpiner observed a young woman with a very toxic diffuse goiter who was operated upon in two stages during the third and fifth months of pregnancy. The patient aborted identical twins three weeks after the second operation, the cord to one of the twins having been obstructed in utero. This twin showed a typical hyperplastic thyroid and the authors conclude that this fetus mirrored the thyroid status of the mother at the time of operation, mechanical factors having altered the character of the blood supply rendering the fetal thyroid inert to change.

Report of Cases

The 19 patients here reported with hyperthyroidism complicating pregnancy averaged 29 years of age (Table II). The oldest was 40, the

TABLE II. THYROID DISEASE COMPLICATING PREGNANCY

Total deliveries 1932-1942		6,112
Thyroid disease complicating pregnancy		19
Oldest patient	40	
Youngest patient	19	
Average age	29	
White patients	18	
Colored patients	1	

youngest 19. Only one in the series was observed in the colored race which corresponds in general to the ratio of colored patients seen on the obstetric service.

Only two patients were seen with hyperthyroidism during their first pregnancy (Table III). The 19 patients comprising this series had had a total of 46 previous pregnancies, or an average of 2.4 children.

TABLE III. PREVIOUS DELIVERIES IN PATIENTS ADMITTED WITH THYROID DISEASE COMPLICATING PREGNANCY

PATIENTS	PREVIOUS PREGNANCIES
2	0
2	1
2	2
4	3
3	4
1	5
2	6
1	7
1	8
1	10
Total 19	46

TABLE IV. EFFECT OF PREVIOUS AND PRESENT PREGNANCY ON THYROID DISEASE

CASE	DURATION GOITER	NO. PREVIOUS PREGNANCIES	ONSET SYMPTOMS	MONTH GESTATION ON ADMISSION	EFFECT PREGNANCY ON THYROID DISEASE	TOXICITY ON ADMISSION
1	9 years	5	Increasing each pregnancy	7	Increasing toxicity	3 plus
2	12 years	4	1 year ago	3	Increasing toxicity	2 plus
3	5 years	1	2 years ago	4½	Increasing toxicity	2 plus
4	5 years	8	5 years ago increasing	9	Increasing toxicity	2 plus
5	6 years	3	Increasing 5 months	8	Increasing toxicity	2 plus
6	8 years	7	3 months ago 7 years ago thyroidectomy	8½	Increasing toxicity	3 plus
7	8 years	1	6 years ago recurrence	7	Increasing toxicity	3 plus
8	20 years	4	Increasing each pregnancy	7	Increasing toxicity	3 plus
9	1 year	0	3 months ago	5	Increasing toxicity	2 plus
10	6 years	10	1 year	1	Increasing toxicity	1 plus
11	2 years	2	2 years	3	Increasing toxicity	2 plus
12	18 months	2	1 year 8 years ago thyroidectomy	4	No increase	1 plus
13	8 years	6	7 years ago recurrence	9	Increasing toxicity	2 plus
14	8 years	6	Increasing 6 years	2	Slight increase	1 plus
15	2 years	3	Increasing 2 years	2	Increasing toxicity	1 plus
16	1 year	0	Increasing 1 year	4	Increasing toxicity	3 plus
17	4 years	3	Increasing 4 months	4	Slight increase	1 plus
18	20 years	3	Gradual increase	6	Slight increase	1 plus
19	8 years	4	Increase 2 years	8	Slight increase	2 plus

Every one of this series of patients had been conscious of the presence of a goiter prior to the onset of pregnancy during which thyrotoxicosis became a real factor. Actual symptoms of hyperthyroidism appeared for the first time during pregnancy in only three cases, the remaining 16 patients having definite evidence of thyrotoxicosis prior to conception. In Table IV is noted the effect of previous and the present pregnancies on the thyroid status. Wallace observed that pregnancy influenced existing thyrotoxicosis in one of three ways:

1. It may definitely improve it in a fair percentage of cases, occasionally permanently.
2. It may neither ameliorate nor aggravate the condition.
3. It may markedly increase the thyrotoxicosis.

Bram found in his series of cases that in 30 per cent the syndrome was not aggravated by pregnancy. In the remaining 70 per cent the thyroid disease was made worse and in 15 per cent spontaneous abortion occurred.

In our series the thyrotoxicosis was definitely aggravated by the pregnancy in 13 cases (74 per cent), slightly increased in four cases (21 per cent), and not affected in one case (5 per cent). Five patients were admitted during the first trimester of pregnancy, 6 during the second and eight during the third. On the basis of clinical toxicity, the patients were divided into three groups, 31 per cent being considered mildly toxic, 42 per cent moderately toxic and 27 per cent acutely ill with marked thyrotoxicosis.

Exophthalmic goiter was the type of thyroid disease present in 10 of the 19 patients, the remaining 9 having adenomatous goiter with secondary hyperthyroidism. In any series of patients with hyperthyroidism complicating pregnancy, exophthalmic goiter is inevitably the most common type encountered because of the age of the patients. The average age of our 9 patients with adenomatous goiter and hyperthyroidism was 32 years, while the 10 women with exophthalmic goiter averaged 27 years of age. Mussey, Plummer, and Boothby[24] have reported that 70 per cent of all patients with exophthalmic goiter are under the age of 40, while approximately the same percentage of patients with adenomatous goiter and hyperthyroidism are over 40 years of age.

A study of the variation in weight experienced by this group of patients was undertaken. Adequate data were available in 10 patients, of whom 6 gave a history of weight loss and 4 had gained. An evaluation of the loss of weight in these 6 cases, averaging 20 pounds, is difficult since all were observed between the second and fifth months of their pregnancy. The thyrotoxicosis present was undoubtedly a factor in their loss in weight, but the nausea and vomiting so frequently seen in these pregnant women with hyperthyroidism must be considered an associated cause. None of the 4 patients with a known gain in weight had increased over that amount which might be expected for their stage in pregnancy.

A correlation of the blood pressure, pulse, basal metabolic readings, and period of gestation in this series of 19 cases is outlined in Table V. Considering a systolic pressure of 140 and a diastolic of 90 as the top limit of normal, 9 patients in the group might be considered to have hypertension. At rest under basal conditions 10 of the 19 patients had a pulse rate of 100 or above after admission to the hospital. The basal metabolic readings were quite difficult to evaluate unless considered with the clinical picture, period of gestation, and history of previous iodine

TABLE V. CORRELATION OF BLOOD PRESSURE, PULSE, BASAL METABOLIC RATE, AND PERIOD GESTATION IN PATIENTS ADMITTED WITH HYPERTHYROIDISM AND PREGNANCY

CASE	AGE	BLOOD PRESSURE	PULSE	B.M.R.	MONTH GESTATION	PREVIOUS TREATMENT	TYPE THYROID DISEASE
1	28	155/0	130	Plus 70	7	None	Adenomatous with hyperthyroidism
2	40	118/80	100	Plus 45	3	None	Adenomatous with hyperthyroidism
3	20	135/75	100	Plus 42	4½	Iodine 3 years	Adenomatous with hyperthyroidism
4	34	160/50	100	?	Term	Iodine 3 years	Adenomatous with hyperthyroidism
5	24	160/90	140	Plus 25	8	None	Adenomatous with hyperthyroidism
6	31	138/70	?	Plus 32	8½	Iodine 3 months	Adenomatous with hyperthyroidism
7	32	200/110	140	Plus 65	7	Thyroidectomy 7 years ago Radium 3 years ago rec.	Exophthalmic goiter
8	40	178/90	160	Plus 57	7	None	Adenomatous with hyperthyroidism
9	27	128/64	84	Plus 29	5	None	Exophthalmic goiter
10	37	145/100	80	Plus 17	1	None	Exophthalmic goiter
11	24	145/60	90	Plus 40	3	X-ray therapy 6 months previous. No benefit	Exophthalmic goiter
12	28	104/50	70	Plus 30	4	Iodine 2 months	Exophthalmic goiter
13	26	120/70	90	Plus 35	9	Thyroidectomy 7 years ago Recurrent 6 years ago	Exophthalmic goiter
14	27	125/75	88	Plus 17	2	Iodine 2 months	Exophthalmic goiter
15	26	140/85	90	Plus 20	2	None	Exophthalmic goiter
16	19	160/75	110	Plus 69	4	None	Exophthalmic goiter
17	25	134/76	100	Plus 12	7	Iodine 6 months	Exophthalmic goiter
18	38	122/78	96	Plus 29	6	Iodine 3 months	Adenomatous with hyperthyroidism
19	33	162/90	110	Plus 62	8	Iodine 3 months	Adenomatous with hyperthyroidism

therapy. The highest basal metabolic rate in the group was plus 70 with the more toxic patients ranging from plus 40 to plus 65. Eight patients had received no therapy for their thyrotoxicosis prior to their hospital admission, while an additional group of 8 had been on Lugol's solution for periods varying from two months to three years. Two patients had previously undergone thyroidectomy seven years before admission with a recurrence in each instance. One of these subsequently had radium therapy elsewhere for her thyrotoxicosis without benefit. X-ray therapy had been employed in one case for the treatment of the hyperthyroidism without improvement prior to conception.

Of the 8 patients admitted to the University Hospital in the last trimester of pregnancy, 5 (62.5 per cent) exhibited the signs of toxemia of pregnancy in one or another of its various forms. Only 1 of the 5 patients presented the classical triad of hypertension, edema, and albuminuria. This was in 1 of the 2 cases of exophthalmic disease. The other 4 patients had hypertension and edema but no albuminuria. These 4 cases occurred in the six instances of adenomatous disease. The true incidence of toxemia occurring in thyroid disease in our series of 19 cases was 26.2 per cent which is considerably lower than that of Javert who reported 76 per cent incidence in 18 cases.

The therapeutic measures employed in this group of 19 patients are outlined in Table VI. Eighteen of the 19 cases have been followed through their pregnancy and for a variable period afterwards. A live baby was obtained in all but one instance and one mother was delivered of twins. There were two maternal deaths in the series.

Eleven patients were treated conservatively with rest, Lugol's solution, and sedatives. In nine instances delivery was uneventful, in one section was done, and the eleventh is now in the hospital in the eighth month of her pregnancy. The 11 babies delivered were all normal excepting two, who were premature but survived. Thyroidectomy has been done in 4 cases since delivery with a satisfactory result in each instance, and will be done during the post-partum period in the one case now in the hospital approaching term. Four of the remaining 6 patients treated conservatively have been followed and in every instance the thyrotoxicosis has subsided and the patients are clinically well. Efforts to trace two patients have been unsuccessful, but at their dismissal following delivery, thyroidectomy was not considered necessary.

Surgical treatment of the hyperthyroidism during pregnancy was advised and carried out in seven cases. Five patients successfully underwent subtotal thyroidectomy; two in the third, one in the fourth, one in the fifth, and one in the sixth month of pregnancy. Each mother subsequently delivered a normal, live child, and has remained well to date, although one has a basal metabolic rate of –41 with mild hypothyroidism. The remaining two desperately ill patients were treated by staged polar ligation in the seventh and eighth months of pregnancy. One was delivered of a normal child at term while in the second instance the baby was stillborn and macerated. A subtotal thyroidectomy was done during the post-partum period in one case with an excellent result and a subsequent pregnancy has been completed without incident. Thyroidectomy following delivery was planned in the second case, but the patient died of a pulmonary embolus on the fourteenth post-partum day.

The other maternal death in this series of 19 cases occurred in a 34-year-old colored woman admitted at term with myocarditis and an

TABLE VI. TREATMENT OUR SERIES PATIENTS WITH HYPERTHYROIDISM COMPLICATING PREGNANCY

CASE	TYPE	TOXICITY	IMMEDIATE TREATMENT	SURGERY BEFORE DELIVERY	LABOR	SURGERY FOLLOWING LABOR	END RESULTS
1	T. A.	3 Plus	Surgery	Polar ligation 2 Stages	Normal Stillborn	Thyroidectomy 2 Stages post Del.	Subsequent pregnancy without difficulty
2	T. A.	2 Plus	Surgery	Thyroidectomy 1 Stage 6th Mo.	Normal Live baby	None	Excellent
3	T. A.	2 Plus	Surgery Admitted	Thyroidectomy 1 Stage 5th Mo.	Normal Live baby Delivery, section	None	Excellent Death on table, P.M.
4	T. A.	2 Plus	At term	None	Live baby		Myocarditis. T.A.
5	T. A.	2 Plus	Conservative	None	Normal 1 Mo. premature	Thyroidectomy 3 Mo. Postpartum	Excellent
6	T. A.	3 Plus	Conservative	None	Delivery, section Live baby	None	Thyroid symptoms subsided
7	X. G.	3 Plus	Conservative	None Pr. Thyroidectomy	Normal 1 Mo. premature	Thyroidectomy 2 Stages 1 Mo. P.P.	Excellent
8	T. A.	3 Plus	Conservative With x-ray	Polar ligation 2 Stages 8th Mo.	Normal Live baby	None	Died 15th post-partum day Pulmonary infarct
9	X. G.	2 Plus	Conservative	None	Normal Live baby	None	Symptoms subsided
10	X. G.	1 Plus	Conservative	None	Normal Live baby	Thyroidectomy 16 Mo. later	Excellent following operation
11	X. G.	2 Plus	Conservative With x-ray	Thyroidectomy 1 Mo. later	Normal Live baby	None	Excellent. B.M.R. -41
12	X. G.	1 Plus	Conservative	None	Normal Live baby	None	Subsequent pregnancy without difficulty
13	X. G.	2 Plus	Conservative	None Pr. Thyroidectomy	Normal Live baby	None	Improved
14	X. G.	1 Plus	Surgery	Thyroidectomy 3rd Mo.	Normal Live baby	None	Improved
15	X. G.	1 Plus	Conservative	None	Normal Live baby	None	Not followed
16	X. G.	3 Plus	Surgery	Thyroidectomy 4th Mo.	Normal Live baby	None	Excellent
17	X. G.	1 Plus	Conservative	None	Normal Live baby	None	Not followed
18	T. A.	1 Plus	Conservative	None	Normal Live twins	Thyroidectomy 2 Yr. later	Excellent
19	T. A.	2 Plus	Conservative	None	In hospital At term	Thyroidectomy to be done post-partum	—

TABLE VII. TREATMENT REPORTED CASES HYPERTHYROIDISM COMPLICATING PREGNANCY

AUTHOR	YEAR	CASES	TYPE		CASES SURGERY BEFORE DELIVERY			PATIENTS TREATED CONSERV.	MIS-CARRIAGES	THERAPEUTIC ABORTIONS	MORTALITY		THYROIDEC-TOMY AFTER DELIVERY
			X. G.	T. A.	X. G.	T. A.	TOTAL				CHILD	MOTHER	
Robinson	1922	15	15	0	0	0	0	15	0	0	0	0	0
Strouse and Daly	1926	61	0	0	0	0	0	61	0	0	0	0	Several
Hyman and Kessel	1927	9	0	0	0	0	0	9	1	0	1	0	0
Yoakam	1928	35	0	0	0	1	1	34	0	0	0	0	0
Clute and Daniels	1929	18	16	2	0	0	15	3	1	0	0	0	3
Plummer, et al.	1929	42	32	10	25	8	32	10	2	0	2	0	0
Fahrni	1930	14	11	3	11	3	14	0	2	0	2	0	0
Mussey and Plummer	1931	41	29	12	22	9	31	10	0	0	1	0	1
Lahey	1931	15	0	0	0	0	15	0	0	0	1	0	0
Frazier and Ulrick	1932	38	0	0	0	0	7	31	0	0	0	0	0
Bothe	1933	10	0	0	0	0	5	5	1	0	0	0	0
Wallace	1933	9	0	0	0	0	0	9	0	3	3	0	0
Portis and Roth	1939	14	0	0	0	0	2	12	0	1	1	0	0
Mussey	1939	66	43	23	29	19	48	18	0	0	0	0	3
Total		387					170	217	7	4	11	0	7

adenomatous goiter with mild hyperthyroidism. She was delivered of a live baby by section but died suddenly on the table. Post-mortem examination showed a large nodular goiter weighing 248 Gm. and a flabby, dilated heart with extensive evidence of myocarditis.

Discussion

The recorded experience of a group of authors with hyperthyroidism complicating pregnancy has been analyzed in Table VII. Of the total of 387 collected cases, 170, or 44 per cent, received surgical therapy for their hyperthyroidism prior to delivery and at least 7 patients required thyroidectomy following delivery. The remaining 217 cases (56 per cent) were treated conservatively. There were 7 recorded miscarriages and 4 therapeutic abortions. Eleven babies in the group died at delivery, an infant mortality of 2 per cent. There was only one recorded maternal death (0.26 per cent).

The opinions expressed in the literature regarding the correct method of managing hyperthyroidism complicating pregnancy have been somewhat divergent. In general there have been those who have favored conservatism in all cases, those who recommend thyroidectomy at any stage in the pregnancy, and a group who feel that every case must be individualized.

With the gradual accumulation of experience with thyrotoxicosis complicating pregnancy, and a better appreciation of the many factors requiring consideration, a definite trend toward individualization of the case is apparent. There can be little doubt that the pregnant woman with hyperthyroidism can successfully withstand a thyroidectomy, but the question remains the necessity and advisability of the procedure in all cases.

The combination of hyperthyroidism and toxemia of pregnancy in the same patient does not demand anything other than conservative therapy. The treatment of one condition in no way conflicts with the treatment of the other. Interruption of pregnancy should be considered only when it would be of definite value to the mother. The time of interruption will have to be individualized. The method used should be the one which will do the patient the least amount of harm and be most likely to result in ultimate recovery of the mother and in the production of a normal live child.

Falls, Hyman and Kessel, Luker, and others have pointed out the frequency with which the syndrome of exophthalmic goiter subsides during the puerperium with complete relief from symptoms. Falls states that one must accept a fetal mortality of 20 per cent from abortion, premature labor and other causes in cases subjected to thyroidectomy during pregnancy, but the collected figures do not appear to substantiate this statement. Hinton[17] has advised interruption of the pregnancy in cases with adenomatous goiter associated with severe hyperthyroidism and myocarditis and in fulminating cases of exophthalmic goiter endangering the life of the mother. He concludes, however, that 90 per cent of the

cases of hyperthyroidism associated with pregnancy can be successfully carried through to normal delivery if properly managed.

Therapeutic abortion is favored by few authors today as a desirable method of relieving the hyperthyroidism. Fletcher has advised sterilization of all patients with hyperthyroidism whose delivery is accomplished by section but this advice may be open to question.

All authors are agreed that adenomatous goiter with hyperthyroidism complicating pregnancy is more serious than exophthalmic goiter but is fortunately less frequent. If the adenomatous goiter is accompanied by pressure symptoms or evidence of myocarditis, surgical therapy is definitely indicated. Four of our seven cases subjected to surgery during pregnancy were of this type and both of our maternal deaths were women with adenomatous goiter and hyperthyroidism. These patients seen near term must be very carefully supervised during their delivery and should have the benefit of thyroidectomy during the puerperium.

The use of iodine as a valuable therapeutic agent in the conservative treatment of hyperthyroidism during pregnancy is now generally accepted. There still exists some question as to its usefulness in adenomatous goiter with hyperthyroidism, but the former opinion that it definitely is contraindicated no longer holds. The value of Lugol's solution in controlling mild hyperthyroidism from exophthalmic goiter complicating pregnancy is now well established. These women tolerate small doses of iodine for prolonged periods during pregnancy, and in conjunction with rest and sedation the symptoms of hyperthyroidism may be adequately controlled until the pregnancy is terminated. Patients with exophthalmic goiter who do not respond to conservative measures may be safely subjected to thyroidectomy at any time this seems indicated. Those who are successfully carried through to the puerperium on conservative measures and who continue to evidence symptoms of hyperthyroidism should then be subjected to thyroidectomy.

Summary and Conclusions

1. A series of 19 cases of hyperthyroidism complicating pregnancy are reported.

2. The incidence of pregnancy in established thyroid disease is over three times as high as the incidence of hyperthyroidism developing during pregnancy.

3. The thyrotoxicosis was definitely aggravated by the pregnancy in 74 per cent of the series, increased in 21 per cent, and unaffected in 5 per cent.

4. Toxemia of pregnancy, varying in degree, occurred in 62.5 per cent of the eight patients admitted during the third trimester.

5. Eleven patients were treated conservatively and eight underwent surgery for their thyroid disease prior to delivery.

6. One fetal death occurred, and there were two maternal deaths in this series.

7. Both maternal deaths occurred in patients with adenomatous goiter and hyperthyroidism, confirming the opinion that this is the most serious type of thyroid disease complicating pregnancy.

8. Thyroidectomy is a safe surgical procedure during pregnancy and should be undertaken at any stage if conservative treatment does not control the thyrotoxicosis.

9. The treatment of the patient with hyperthyroidism complicating pregnancy should be individualized. Surgical interference will be necessary more frequently in patients with adenomatous goiter and hyperthyroidism than in those with primary exophthalmic goiter.

References

1. Bothe, F. A.: Am. J. Obst. & Gynec. **25**: 628, 1933.
2. Bothe, F. A.: Ann. Surg. **101**: 422, 1935.
3. Bram, I.: Pennsylvania M. J. **39**: 239, 1936.
4. Clute, H. M., and Daniels, D. H.: Am. J. M. Sc. **179**: 477, 1930.
5. Colvin, E. D., and Bartholomew, R. A.: Am. J. Obst. & Gynec. **37**: 584, 1939.
6. Cornell, E. L.: Surg., Gynec. & Obst. **36**: 53, 1923.
7. Dean, J. R.: Canad. M. A. J. **17**: 1355, 1927.
8. Enright, L., Cole, V. V., and Hitchcock, F. A.: Am. J. Physiol. **113**: 221, 1935.
9. Fahrni, G. S.: Canad. M. A. J. **23**: 645, 1930.
10. Falls, F. H.: Northwest Med. **28**: 391, 1929.
11. Fleischer, A. J.: Am. J. Obst. & Gynec. **22**: 273, 1931.
12. Frazier, C. H., and Ulrick, H. F.: Am. J. Obst. & Gynec. **24**: 870, 1932.
13. Gardiner-Hill, H.: Lancet **216**: 120, 1929.
14. Hanna, G. C., Jr.: Am. J. Obst. & Gynec. **35**: 115, 1938.
15. Hewitt, W. F., Jr., and Van Liere, E. J.: Endocrinology **28**: 62, 1941.
16. Hinton, J. W.: Am. J. Obst. & Gynec. **13**: 204, 1927.
17. Hinton, J. W.: Am. J. Obst. & Gynec. **20**: 183, 1930.
18. Hughes, E. C.: New York State J. Med. **34**: 873, 1934.
19. Hughes, E. C.: Am. J. Obst. & Gynec. **40**: 48, 1940.
20. Hyman, H. T., and Kessel, L.: J. A. M. A. **88**: 2032, 1927.
21. Javert, C. T.: Am. J. Obst. & Gynec. **39**: 954, 1940.
22. Lahey, F. A.: New York State J. Med. **31**: 405, 1931.
23. Luker, S. G.: Proc. Royal Soc. Med. **26**: 96, 1932.
24. Mussey, R. D., Plummer, W. A., and Boothby, W. M.: J. A. M. A. **87**: 1009, 1926.
25. Mussey, R. D.: Am. J. Obst. & Gynec. **36**: 529, 1938.
26. Mussey, R. D., and Plummer, W. A.: J. A. M. A. **97**: 602, 1931.
27. Mussey, R. D.: Proc. Staff. Meet. Mayo Clinic **14**: 205, 1939.
28. Mussey, R. D.: J. Michigan M. Soc. **38**: 295, 1939.
29. Phatak, N. M., Zener, F. B., and David, N. A.: Proc. Soc. Exper. Biol. & Med. **45**: 667, 1940.
30. Plass, E. D., and Yoakam, W. A.: Am. J. Obst. & Gynec. **18**: 556, 1929.
31. Portis, B., and Roth, H. A.: J. A. M. A. **113**: 895, 1939.
32. Robinson, A. L.: J. Obst. & Gynaec., Brit. Emp. **29**: 296, 1922.
33. Root, H. K., and Root, H. F.: Arch. Int. Med. **32**: 411, 1923.
34. Sandiford, I., and Wheeler, T.: J. Biol. Chem. **62**: 329, 1924.
35. Soule, S. D.: Am. J. Obst. & Gynec. **23**: 165, 1932.
36. Strouse, S., and Daly, P. A.: Wisconsin M. J. **25**: 325, 1926.
37. Wallace, J. T.: Am. J. Obst. & Gynec. **26**: 77, 1933.
38. Warren, S., and Shpiner, L. B.: J. A. M. A. **109**: 575, 1937.
39. Yoakam, W. A.: Am. J. Obst. & Gynec. **15**: 617, 1928.

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ACTION OF MORPHINE IN OBSTETRIC ANALGESIA*

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THE present investigation represents an attempt to determine under conditions of laboratory control the action upon the fetus of morphine and its effect upon the mechanism of labor. Under clinical conditions the administration of morphine for the relief of pain during labor is attended by so many variable factors, especially those which are unforeseen, that the hazard of injury to the child or mother has remained obscure. Despite the considerable knowledge of the action of morphine which the pharmacologist has provided, the evidence from the obstetric standpoint is incomplete.

Furthermore, quantitative evaluation of the hazard of morphine during labor, not merely the recognition of the existence of such risk, is urgent in the measure that relief of pain is required. By analysis of the action of morphine, therefore, the aim is to work out a standard method of assay by which other drugs which are proposed for use in obstetrical analgesia may be compared with morphine.

Methods and Material

In the present experiments rabbits were selected for study. The response to morphine in this species is favorable for comparison with man. The animals were reared in the laboratory and were from selected stock which had been under supervision for many years. A standard diet of alfalfa, hay, oats, and cabbage was fed.

In order to eliminate the factor of the complications of labor, the effect of morphine upon the fetus was investigated by three methods. First, the effect on fetal respiratory movements was observed in animals prepared according to a technique previously described (Snyder and Rosenfeld, 1937) which permitted correlation of the effect on the maternal animals such as analgesia or respiratory depression, with that on the fetuses as seen through the wall of the unopened uterus. Second, the state of the fetuses was determined upon delivery by hysterotomy at various intervals varying from twelve minutes to fifteen hours after intravenous injection of the maternal animal. Third, following injection of the maternal animal the influence of morphine upon the resistance of the fetus to anoxia was measured in terms of the duration of respiratory movements when nitrogen was breathed instead of air, following delivery by hysterotomy. In addition, normal fetuses were

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injected directly with morphine and the time of survival in nitrogen was determined, using apparatus previously described (Rosenfeld and Snyder, 1938).

In order to determine the effect of morphine upon labor, the incidence of stillborn fetuses was observed following passage through the birth canal. The time of mating and ovulation were known accurately and morphine was injected exactly thirty-one days after mating. The length of pregnancy averaged thirty-two days in animals of this stock. One series of rabbits was injected at an earlier stage, namely, twenty-six days. Throughout pregnancy the animals were isolated in separate cages. Litters containing one or two fetuses were not included.

Morphine sulfate was used throughout, being injected into the ear vein during a period of one minute in a volume of 2 c.c. of distilled water. Dosage is expressed by weight of morphine sulfate and not of the alkaloid base.

According to Eddy, the minimal effective dose of morphine for respiratory effect in rabbits is 0.20 mg. per kg. morphine sulfate which is equivalent to 0.15 mg. per kg. alkaloid base; and for analgesic effect, using cats, the dose is 1 mg. per kg. morphine sulfate (0.75 mg. per kg. alkaloid base). Furthermore a striking inhibition of elimination of fecal contents from the alimentary tract was observed following dosage of 5 mg. per kg. morphine sulfate in rabbits and dogs. In our animals a definite analgesic effect was evident in the maternal animal following 1 mg. per kg. morphine sulfate.

In attempting to correlate the response to morphine in man and in the rabbit, it is of interest to note that the basal metabolic rate of the rabbit is 3 times greater than that of man, the oxygen consumption per kilogram per hour at rest being about 200 c.c. in man, in contrast to 650 c.c. in the rabbit (Krogh, 1940). Thus, a total dose of 16 mg. of morphine sulfate in a man of 70 kg. amounts to 0.23 mg. per kg., or if multiplied by 3, is three quarters of the dose used for analgesia in the rabbit.

The Effect of Morphine on the Fetus

Effect of Morphine Upon Fetal Respiration.—Changes in rate of intrauterine respiratory movements observed directly through the wall of the unopened rabbit uterus at full term afford a sensitive indicator for the detection of the earliest effect of narcosis in the fetus following administration of morphine to the maternal animal (Rosenfeld and Snyder, 1939). The degree and duration of respiratory depression permit evaluation in roughly quantitative terms of the extent to which a particular narcotic affects the fetus. Comparison by this method of morphine with other nonvolatile drugs, such as chloral hydrate, paraldehyde, and pentobarbital sodium revealed certain advantages of morphine.

In the light of these findings, observations were extended upon morphine as well as certain new derivatives of exceptional analgesic potency, available through the courtesy of the Committee on Drug Addiction, National Research Council (Snyder and Lim, 1941). With regard to morphine, it was found that respiratory movements of the fetuses were not abolished by a dosage which produced definite analgesia and respiratory depression in the maternal animal. Thus in a typical experiment a dose of 1 mg. per kg. of morphine sulfate intravenously in the

maternal animal was repeated three times at intervals of twenty minutes, and finally a dose of 10 times the initial one was given. Seven litters including 42 fetuses were observed. Depression of intrauterine respiratory movements may occur as the dose is increased and occasionally there is a transient interruption of rhythmical respiration. The outstanding result during observation of two hours or longer was the rhythmical breathing of the fetuses despite administration to the mother of 13 times the analgesic dose of morphine.

Furthermore, delivery of the fetuses by hysterotomy after several hours observation within the uterus was followed by rapid respiratory movements at birth. It was evident that marked depression of intrauterine respiration even involving a period of apnea as a result of narcosis did not necessarily produce irreversible damage of the respiratory system.

Effect of Morphine Upon the Fetus at Various Intervals After Injection.—In order to determine the effect upon the fetuses of a large dose of morphine (13 mg. per kg.) or about 13 times the dose required for an analgesic effect in the maternal animal, a series of sixteen animals was injected intravenously and the fetuses were delivered by hysterotomy at various intervals from twelve minutes to fifteen hours after administration of the drug. The litters were at term except in four animals which were delivered at a stage of prematurity. Hysterotomy was accomplished under novocain infiltration, thus avoiding a general anesthetic (Table I).

TABLE I. DELIVERY BY HYSTEROTOMY

RABBIT	STAGE OF PREGNANCY (DAYS)	DOSAGE OF MORPHINE I.V.		TIME ELAPSED FROM INJECTION UNTIL DELIVERY	FETUSES	
		MG./KG.	TOTAL MG.		ALIVE AND SURVIVED	DEAD
1	31	13	35	15 hr.	8	0
2	31	13	35	14 hr.	7	0
3	31	13	42	13 hr.	5	0
4	31	13	38	12½ hr.	5	1
5	31	13	39	1 hr.	5	0
6	32	13	41	40 min.	8	0
7	28	12	37	35 min.	9	0
8	29	13	35	35 min.	7	0
9	30	13	30	35 min.	5	0
10	30	13	41	30 min.	2	0
11	31	13	44	30 min.	1	0
12	31	13	44	30 min.	6	0
13	31	13	40	25 min.	4	0
14	32	13	31	20 min.	7	0
15	33	13	38	16 min.	4	0
16	32	13	32	12 min.	3	0

The outstanding result in a consecutive series of 86 fetuses was the survival of the entire group of fetuses following operative delivery. Only one fetus of the series was found dead within the uterus, and in this instance separation of the placenta with a large retroplacental hematoma was involved rather than fetal narcosis. The remaining five fetuses of this litter were alive and survived.

The fetuses at delivery showed marked differences in activity according to the interval which elapsed following administration of morphine.

In litters at term which were delivered less than one-half hour following intravenous injection of the maternal animal, the fetuses showed marked signs of narcosis, body movements were sluggish, response to stimulation was retarded, and respiratory activity was depressed. In the fetuses delivered at a later time within the first hour after injection no further increase in degree of narcosis was noted. It is interesting to note that among this group were included twenty-three fetuses delivered at a stage of prematurity. In the litters delivered twelve to fifteen hours after morphine, the fetuses crawled about and attempted to suckle, their activity being indistinguishable from that of untreated controls.

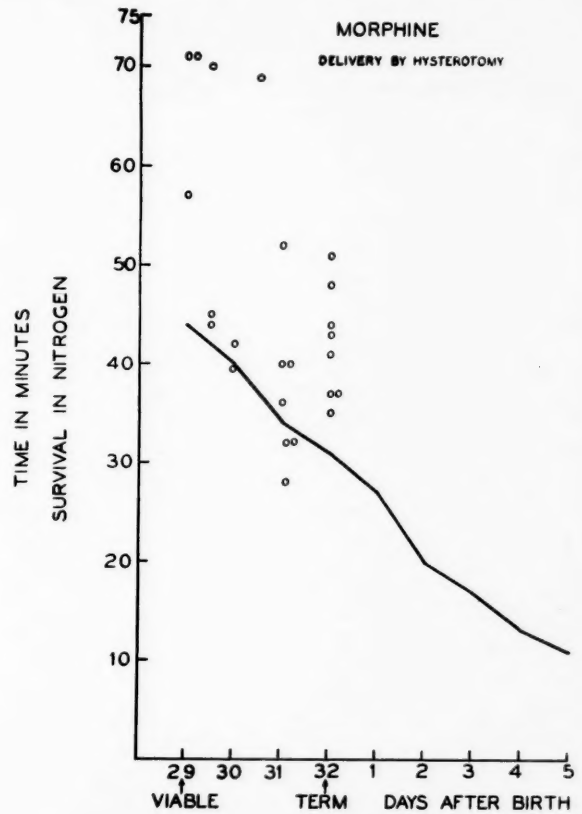

Fig. 1.—Effect of morphine on resistance of the fetus to anoxia. Circles show duration of respiratory movements of fetuses in nitrogen, the survival time being prolonged rather than shortened. The base line is the average survival time in a series of 200 normal fetuses. The maternal animal received morphine, 13 mg. per kg., intravenously about one-half hour before hysterotomy.

In the foregoing series of animals delivery by hysterotomy eliminated the factor of labor and thus permitted evaluation of the effect of narcosis of the fetus following morphine entirely independent of the complications which attend delivery through the birth canal. It is of particular significance from this standpoint that administration of large doses of morphine sufficient to cause deep analgesia of the maternal animal did not result in intrauterine death of the fetuses or in failure

to survive after birth, even though delivery occurred at short intervals after injection when narcosis of the fetus was at a maximum.

The Effect of Morphine Upon the Resistance of the Fetus to Asphyxia. —Delivery by Hysterotomy After Administration of Morphine to the Maternal Animal: In view of the depression of respiratory movements and the sluggish motor responses following morphine, the question arose as to whether or not the defense of the fetuses against oxygen want was impaired by morphine narcosis. This point could readily be determined, since a base line of normal values was available, giving the time of survival in nitrogen of rabbits delivered at term or prematurely (Glass and Snyder, 1942). With the apparatus described previously (Rosenfeld and Snyder, 1938), kymograph records of the respiratory

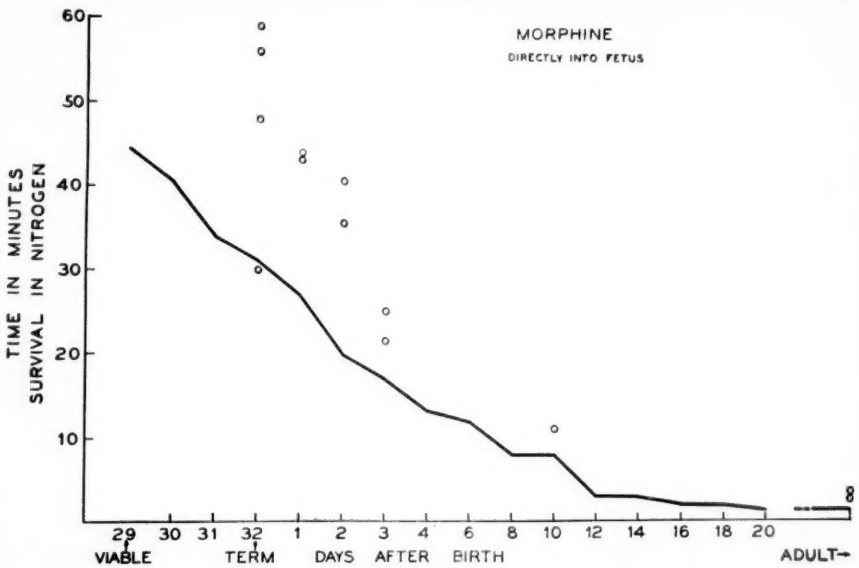

Fig. 2.—Effect of morphine on resistance of the fetus to anoxia. Morphine, 13 mg. per kg., was injected intravenously about one hour before breathing of nitrogen began.

excursions of fetuses which were breathing nitrogen instead of air were obtained by aid of a plethysmograph connected to a recording tambour. Following administration of morphine (13 mg. per kg.) intravenously to the maternal animal, the entire litter of fetuses were delivered by hysterotomy (after local novocain infiltration) at intervals of twelve to forty minutes after injection. Observations were made successively on about three fetuses of a litter. Results were based upon twenty-four fetuses from nine litters delivered at twenty-nine to thirty-two days (Fig. 1).

Observations showed that after morphine, there was no decrease in the time of survival of fetuses when breathing nitrogen instead of air. Contrary to common belief, it was found that respiration continued for a longer time in the fetuses which were under the influence of morphine than in those in the series of normal controls.

Furthermore, these findings were supported by observations on the remaining fetuses of the litter one or two days after delivery, when narcosis was no longer evident. In six fetuses obtained from three

litters twenty-one hours or more after delivery, the time of survival in nitrogen was markedly shortened in contrast to that observed during narcosis.

Direct Injection of Morphine Into the Fetus.—The effect of morphine upon the tolerance to anoxia was further tested by direct injection of morphine (13 mg. per kg.) intravenously in the newborn rabbit. The animals were exposed to nitrogen within an hour following injection and respiratory tracings were obtained as previously described. Observations on thirteen animals in which nitrogen was breathed instead of air revealed no decrease in time of survival after direct injection of morphine. In fact, respiration continued for a longer time in this group than in normal controls (Fig. 2).

The Effect of Morphine on Labor

Striking evidence of the effect of morphine on the labor mechanism is afforded by increased incidence of stillbirths when the fetuses are expelled through the birth canal in contrast to delivery by hysterotomy. Following the injection of a large dose of morphine (13 mg. per kg.) at thirty-one days which is about the time of the onset of labor, spontaneous parturition involving a total number of 217 fetuses resulted in the birth of 93 living and 124 dead ones, or a fetal mortality of 57 per cent. In contrast, in a control series of 260 births occurring spontaneously in which morphine was not injected, there were 228 living and only 32 stillborn, or a fetal mortality of 12 per cent (Table II).

TABLE II. SPONTANEOUS BIRTH

MORPHINE DOSAGE MG./KG.	STAGE OF PREGNANCY AT INJECTION (DAYS)	STATE OF FETUSES AT BIRTH		FETAL MORTALITY (PER CENT)	TOTAL NUMBER OF FETUSES
		ALIVE	DEAD		
None	--	228	32	12	260
13	31	93	124	57	217
13	26	121	17	12	138
1	31	212	63	23	275

Furthermore, the administration of morphine at an earlier stage of pregnancy, i.e., twenty-six days, was followed by no marked increase in stillbirths such as occurred after injection at the time of labor. In animals injected at twenty-six days with 13 mg. per kg. of morphine, in a series of 138 births, there were 121 living and 17 dead fetuses, or a fetal mortality of 12 per cent.

There was evidence that increase in stillbirths followed the administration at the time of labor of even a small dose of morphine, i.e., 1 mg. per kg., or approximately the amount which is required to elicit analgesia. Following injection of 1 mg. per kg., of morphine at thirty-one days, in a total series of 275 births, there were 212 living and 63 dead fetuses, or a fetal mortality of 23 per cent.

Analysis of the distribution of stillbirths among various litters of the series throws light upon the manner in which morphine influences the labor mechanism. Stillbirths do not occur uniformly among the litters

of a series but rather are grouped chiefly in certain litters. In this connection it is interesting to consider the frequency with which labor is attended by the expulsion of at least three dead fetuses in a litter, a number which is definitely in excess of the average incidence (Table III).

TABLE III. SPONTANEOUS BIRTH

MORPHINE MG./KG.	STAGE OF PREGNANCY AT INJECTION (DAYS)	LITTERS			STILLBORN FETUSES				PROLONGED LABOR	
		TOTAL	WITH EXCESSIVE STILLBIRTHS		TOTAL		PORTION IN LITTERS WITH EXCESSIVE STILLBIRTHS			
			NO.	%	NO.	%	NO.	%	NO.	%
None	--	41	5	12	32	12	24	75	4	10
13	31	32	19	59	124	57	111	89	13	41
13	26	20	2	10	17	12	12	71	0	0
1	31	44	9	20	63	23	49	78	7	16

First, in the series of control animals in which morphine was not injected, in the course of spontaneous delivery of 41 litters there were five litters, or 12 per cent, which had three or more stillborn fetuses. Second, in animals in which a large dose of morphine (13 mg. per kg.) was given at thirty-one days in the birth of 32 litters, there were 19 litters, or 59 per cent, in which at least three fetuses were dead at birth. Third, in the series of 20 litters in which 13 mg. per kg. of morphine was injected at twenty-six days, there were only two litters, or 10 per cent, which had at least three stillborn fetuses. Fourth, in animals in which a small dose of morphine (1 mg. per kg.) was given about the time of labor (thirty-one days), in a series of 44 litters there were nine litters, or 20 per cent, which had three or more stillborn fetuses. It was evident that the frequency of the occurrence of labor which was so altered as to result in three or more stillborn fetuses in a litter corresponded closely to the frequency of occurrence of stillborn fetuses. Thus, in the four groups of animals cited above, labor was marked by excessive stillbirths in 12 per cent, 59 per cent, 10 per cent, and 20 per cent of the litters, respectively, while the fetal mortality of the corresponding groups was 12 per cent, 57 per cent, 12 per cent, and 23 per cent.

Furthermore it was interesting to note how many of the stillborn fetuses were found in litters having excessive stillbirths. Thus, in the control series of 260 fetuses, there were 32 stillborn, or 12 per cent; of these 32 dead fetuses, 24, or 75 per cent, belonged to litters which had at least three stillborn. In the series of 217 fetuses born after injection of 13 mg. per kg. of morphine at thirty-one days, there were 124 dead, or 57 per cent; of these 124 stillborn, 111, or 89 per cent, occurred in litters which had three or more stillborn. In the series of 138 fetuses born after the injection of 13 mg. per kg. of morphine at twenty-six days, there were 17 stillborn or 12 per cent; of these 17 dead fetuses, 12, or 71 per cent, were in litters which had at least three stillborn. Finally, in the series of 275 fetuses born after a dose of 1 mg. per kg. of morphine at thirty-one days, there were 63 stillborn, or 23 per cent; of these 63 dead fetuses, 49, or 78 per cent, were in litters which had three or more stillborn fetuses.

Marked prolongation of labor increased in frequency following the administration of morphine at the time of labor. Usually a litter of rabbits is born in less than an hour, while after injection of morphine at thirty-one days, expulsion of fetuses during a period of six to thirty-six hours was not uncommon. Thus following 13 mg. per kg. of morphine at thirty-one days, in a series of 23 litters, marked prolongation of labor was noted in 13 litters, or 41 per cent. In contrast, in a control series of 41 litters in which morphine was not injected, prolongation of labor was observed in four litters, or only 10 per cent. After 1 mg. per kg. of morphine or approximately the analgesic dose, injected at thirty-one days in a series of 44 litters, prolonged labor was seen in 7 litters, or 16 per cent. No increase in incidence of prolonged labor was noted, however, when large doses of morphine (13 mg. per kg.) were given about a week before term, e.g., at twenty-six days.

Discussion

From the foregoing findings it was evident that following the injection of morphine in large dosage there was a striking increase in fetal mortality and in the incidence of prolonged labor, when the drug was administered at the time of the onset of labor. In contrast, when the same amount of morphine was given five days before the onset of labor, no such effect was noted.

In explanation of the influence of morphine upon the emptying of the uterus it is interesting to bear in mind the striking effect of this drug upon the emptying of the alimentary canal. Evacuation of the contents of the bowel was delayed twenty-four hours in dogs following morphine in dosage of 6 mg. per kg. (Kreuger, 1937). In rabbits, Eddy (1932) found that the minimal effective dose for suppression of gastrointestinal evacuation was 6 mg. per kg. of morphine. Furthermore, there was evidence that the suppression obtained with morphine was a specific effect upon gastrointestinal activity rather than the result of general depression induced by the narcotic, since the administration of definitely depressant doses of various hypnotics failed to suppress intestinal evacuation, for example, di-ethyl barbituric acid 100 mg. per kg., or chloral hydrate 150 mg. per kg. In the human being, the medicinal use of opium for the alleviation of diarrhea has been recognized for centuries.

How frequently the labor mechanism fails to function at a level of activity adequate for the birth of living offspring was revealed in the series of uninjected animals, in which 12 per cent of the pregnancies terminated with excessive stillbirths. In this group of 12 per cent of the animals, there occurred 75 per cent of the stillbirths. There was evidence that death occurred at the time of parturition since the fetuses were of full-term development, rarely macerated, and at autopsy no gross defects were noted upon macroscopic examination.

After the administration of morphine 13 mg. per kg., about the time of onset of labor, there was evidence of an increase in the functional failure of the birth mechanism to the extent that 59 per cent of the

pregnancies terminated with excessive stillbirths instead of 12 per cent. Examination of the dead fetuses showed that they had been alive before parturition. In this group of 59 per cent of the animals, there occurred 89 per cent of the stillbirths. It was evident that following morphine the increased number of stillborn fetuses were not uniformly distributed among all of the injected animals but, on the contrary, stillbirths were grouped chiefly in certain animals.

It is interesting to note the effect upon the functional efficiency of the labor mechanisms of morphine in dosage of 1 mg. per kg. which results in definite analgesia in rabbits and is within the range of dosage employed therapeutically. Pregnancy terminated with excessive stillbirths about twice as frequently as in uninjected controls, and the fetal mortality likewise was doubled in this series.

Additional evidence that the increased incidence of fetal mortality was not a direct effect of the action of morphine upon the fetus but rather resulted from injury of the mechanism of labor was obtained by direct observation of fetuses under conditions which eliminated the complications of labor, while keeping constant the dosage level of morphine. For example, following a large dose of morphine the fetuses were alive and survived when delivered by hysterotomy instead of by extrusion through the birth canal. Similarly, the persistence of fetal respiratory movements following injection was observed directly through the wall of the unopened uterus. Direct injection of fetuses with morphine 13 mg. per kg. following delivery did not result in death. In fact, in experiments in which the resistance to asphyxia was tested by the breathing of nitrogen instead of air, the time of survival of the fetuses injected with morphine was not less than that of normal controls.

From the pharmacologic standpoint the present experiments illustrate methods for the laboratory assay of drugs proposed for use in obstetric analgesia. As applied in the case of morphine, two findings especially stand out. First, the action of morphine on the labor mechanism as revealed by increase in fetal mortality brings to light a striking effect on the maternal organism. Second, in the case of the effect of morphine upon the fetus, especially noteworthy is the evidence of the resistance of the fetus to asphyxia under conditions of the experiments despite large dosage of morphine.

Clinically, so far as the findings in the rabbit have a bearing, it is evident that the functional efficiency of the labor mechanism is of prime interest in the problem of obstetric analgesia. Since the question as to whether or not the labor mechanism is normal ultimately depends upon direct observation during labor, it is clear that familiarity with pharmacologic findings regarding the average analgesic dose of the drug may not reveal fully the hazards of use during labor. Knowledge of the course of labor is of first importance in the practice of obstetric analgesia.

Summary

1. Increased incidence of stillbirths following the administration of morphine during labor in rabbits is due to the effect upon the mechanism of labor chiefly, rather than to a direct effect upon the fetus.

2. Fetal mortality in the birth of 890 fetuses obtained from 137 litters was as follows: (1) normal controls, 12 per cent; (2) after morphine 13 mg. per kg. at thirty-one days, i.e., the onset of labor, 57 per cent; after morphine 13 mg. per kg. at twenty-six days, i.e., before the onset of labor, 12 per cent; after morphine 1 mg. per kg., i.e., an analgesic dose, at thirty-one days, 23 per cent.

3. Stillbirths were not uniformly distributed but involved chiefly certain litters as follows: (1) normal controls 12 per cent of the litters; (2) after morphine, 13 mg. per kg., at thirty-one days, 59 per cent; after morphine, 13 mg. per kg., at twenty-six days, 10 per cent; after morphine, 1 mg. per kg., at thirty-one days, 20 per cent of the litters.

Similarly, marked prolongation of labor was noted in certain litters, the incidence being, respectively: (1) 10 per cent, (2) 41 per cent, (3) none, and (4) 16 per cent.

4. Prior to the onset of labor, the fetuses were alive and survived despite administration of morphine to the maternal animal in large dosage (13 mg. per kg.), as shown in the following experiments:

a. By direct observation of intrauterine respiratory movements during a period of two hours or longer, it was found that rhythmical breathing of the fetuses was depressed but not abolished.

b. By hysterotomy, in contrast to expulsion through the birth canal, fetuses were regularly delivered alive at intervals of twelve minutes to fifteen hours following injection.

c. By measurement of the time of survival of fetuses when breathing nitrogen instead of air, it was found that following morphine the resistance to anoxia was not decreased.

5. In considering the clinical use of morphine in obstetric analgesia, it is of interest to note that under controlled experimental conditions morphine definitely increased fetal mortality by injury of the mechanism of labor and, following a dosage within the range employed therapeutically, the frequency of labor with unfavorable outcome was doubled. Since prognosis regarding the functional efficiency of the labor mechanism depends upon direct observation during labor, it is clear that there is reason to limit administration of morphine until evidence of normal function is obtained.

References

1. Rosenfeld, M., and Snyder, F. F.: Am. J. Obst. & Gynec. **38:** 424, 1939.
2. Snyder, F. F., and Rosenfeld, M.: Am. J. Physiol. **119:** 153, 1937.
3. Rosenfeld, M., and Snyder, F. F.: Am. J. Physiol. **121:** 242, 1938.

4. Small, L. F., Eddy, N. B., Mosettig, E., and Himmelsbach, C. K.: Studies on Drug Addiction. Supplement No. *138* to the Public Health Reports. U. S. Government Printing Office, Washington, D. C., 1938.
5. Krogh, A.: The Comparative Physiology of Respiratory Mechanisms, Philadelphia, University of Pennsylvania Press, 1940.
6. Snyder, F. F., and Lim, K. T.: J. Pharmacol. & Exper. Therap. **72**: 39, 1941.
7. Glass, H., and Snyder, F. F.: Anat. Rec. **82**: 465, 1942.
8. Kreuger, H.: Physiol. Rev. **17**: 618, 1937.
9. Eddy, N. B.: J. Pharmacol. & Exper. Therap. **45**: 339, 1932.

THE NATURE AND SIGNIFICANCE OF THE GROOVED NUCLEI OF BRENNER TUMORS AND WALTHARD CELL ISLANDS

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THE nuclei of the epithelial cells found in a Brenner tumor show a characteristic longitudinal grooving or folding that makes them resemble the kernels of the breakfast cereal known as "Puffed Wheat" (Fig. 1). This appearance is conspicuous when the ordinary high power of the compound microscope is employed.* It is strange that the numerous descriptions published in the last ten years concerning this tumor have mostly ignored this strikingly obvious feature. One might assume that "study" of the tumor has in most cases been restricted to low-power inspection.

Varangot (1938) was apparently the first to mention specifically the frequent occurrence of what he interpreted to be "*une sorte de bâtonnet allongé suivant le grand axe du noyaux et le divisant en deux parties.*" But before the time of his publication, and since, this "rod" has appeared in photomicrographs illustrating the tumor (*e.g.*, Meyer, 1932; Plaut, 1933; Gnassi, 1937; Timmerberg, 1939; Hicks, 1941; Grayzel and Friedman, 1941). Recently Danforth (1942a), unaware of Varangot's publication,† has described this feature as a new discovery and has furnished excellent photographs and drawings to illustrate its appearance in both Brenner tumors and Walthard cell islands. Previously, in a communication to me, Dr. Danforth had independently made the same interpretation of this marking as did Varangot, by referring to the nucleus as showing a "line" or "rod." In reply, I pointed out that this was not the case. On the contrary, the appearance was more like a plate, whereas careful study indicated that the effect was produced by folding, although in many instances the adjoining surfaces were closely approx-

*In experiments with controlled staining the marking was found to be visible regardless of the intensity of the stain. It was even plainly discernible in unstained sections. These results do not agree with Danforth's (1942a) conclusion as to visibility only under optimum conditions.

†While Danforth's article was in press I informed him of the existence and nature of Varangot's contribution and he has since acknowledged Varangot's priority in a letter to this JOURNAL (1942b).

imated. In his publication Dr. Danforth has characterized the nucleus as exhibiting a groove or fold.

The presence of this structural peculiarity in the nucleus of the cells of Brenner tumors and Walthard islands is sufficiently well established and is easily verifiable. The frequency of occurrence is variable. In many specimens of Brenner tumors these deformed nuclei are so abundant that almost every nucleus seen is an example (Fig. 1); in other samples they are sparse. In some tumors they are common in certain regions and rare in others. It seems highly improbable from the 11 specimens I have examined that Varangot's generalization (from the study of three specimens) that such nuclei are more numerous at the extreme periphery of the cell cords would stand the test of statistical enumeration.

Rather than to dwell further on these general matters it is my purpose to present some detailed information on the nature of this type of nuclear deformation and on its occurrence and possible significance in these tumors and elsewhere. Many authors have described the Brenner tumor cells as being arranged in a pavement epithelium, but this is obviously incorrect with respect to any ordinary meaning of this term. Since the cells are grouped in cords and masses, they are polyhedral in shape, and when not influenced by some modifying influence they are isodiametric. Lewis (1933) has proved that epithelial cells, subject only to equalized mutual pressures, tend to assume a 14-surfaced shape that in section appears most commonly as a six-sided figure. Such a section naturally resembles a flat, pavement epithelium in surface view. At the extreme periphery of a cord, the outermost cells frequently do assume the nature of a somewhat flattened basal layer. The granular cytoplasm is reticular to alveolar in texture and stains lightly in a neutrophilic manner. Cell boundaries are often indistinct to the point of becoming lost in a syncytium. A shrinkage space rather characteristically surrounds the nucleus. The ovoid nucleus is not small, as sometimes described, but measures up to 6 by 10μ. The notion of smallness, perhaps, comes from cross sections, and especially from the divided appearance in some of these (Fig. 5, *c*, *e*, *g*). The nucleus contains many small chromatin masses, and usually a single, prominent, rounded nucleus. Varangot (1938) is wrong in his assertion of the general occurrence of several nucleoli, although two nucleoli are not uncommon (Fig. 1, *i*). He has presumably included karyosomes among his "nucleoli."

The distinctive alteration of the nucleus, already mentioned, is the result of grooving or infolding. The details of this phenomenon are best seen by the use of an apochromatic oil immersion lens with compensating oculars in a binocular microscope, but such equipment is not wholly necessary. When a nucleus is viewed lengthwise and at a slight slant, the appearance is that of a single line or plate. On focusing, this may prove to be one margin overriding another surface (Fig. 1, *c*, *f*, *g*, *j*, *n*).

The marking usually does not extend the full length of the nucleus (*a, b, c*) and may be curved (*a, j*). At one pole the nucleus is frequently bifid, the converging margins of the notch continuing as the median, longitudinal plate (*b, c, g, k, n*). But both ends may be involved, in which case the appearance is somewhat like that of a complete coffee bean (*f, l*).

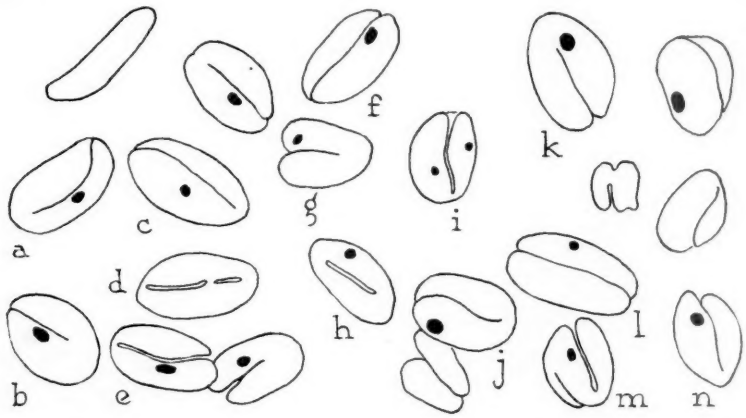

Fig. 1.—The nuclei of a Brenner tumor, as they occurred in a small area of a section. Cell outlines and chromatin masses have been omitted. Camera lucida drawings; ×1500.

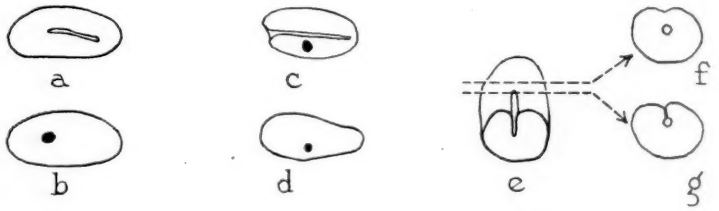

Fig. 2.—Changing appearances of Brenner nuclei, due to focusing. A high and low focus on the same nucleus is shown in *a* and *b*. A similar change produced by focusing is illustrated in *c* and *d*. Three different appearances of the same nucleus, transversely sectioned, are shown in *e, f,* and *g;* to section *c,* half of the nucleus has been added and broken lines indicate the levels of sections *f* and *g*. Camera lucida drawings; ×1500.

Fig. 3.—Transverse sections of Brenner nuclei, showing grooves and "plates." Camera lucida drawings; ×1500.

In direct view, the line- or platelike appearance can be resolved under favorable conditions into a double line (Fig. 1, *e, h, i*). This may be of longer or shorter extent and at times two grooves can be seen in line, but separated (*d*). The parallel lines are really the margins of a local groove or fold, as focusing proves (Fig. 2, *a, b* and *c, d*). This groove extends into the nucleus to varying depths (Figs. 3, *a* and 5, *a, d*). Its longitudinal excursion may include the whole length of the nucleus; the

extent may pass from one end part way toward the other (Fig. 2, *c*); or it may be without relation to either end (*a*). The ends of the groove may extend tunnel-like for a short distance into the interior of the nucleus (Fig. 2, *e-g*). This is a type of canalization. In my experience, indentations of the nuclear membrane are even more plainly seen as double lines in the Sertoli nuclei than in Brenner tumors.

The next question is whether all the markings are caused by grooves, or whether some of them correspond to superficial lines (linear thickenings of the nuclear membrane) and solid plates grown inward from such local thickenings, as Regaud (1900; 1901) believed to be the case in Sertoli nuclei. It is my belief that the fundamental process is grooving or folding. The evidence, best obtained from transverse sections, for this conclusion is as follows: (1) Shallow notches are commonly seen (Fig. 3, *a*), but no local thickenings of the nuclear membrane have been observed and no solid plates as short as the shortest notches; (2) grooves are far more evident than in random surface views of the nuclei; (3) grooves are more common than plates; (4) a "plate" tends to be thicker than the ordinary nuclear wall (Fig. 3, *b, e*); and (5) the plate may separate along its deep border and become a tube, or even a double tube (Fig. 3, *d, e*). If solid plates grow in from the nuclear membrane, one would expect to find early stages of them, but these are lacking. A plate would not necessarily have to be twice as thick as the nuclear membrane, but if a "plate" is produced by the approximation of the two walls of a fold, then the combined walls would have the thickness observed. A surface notch that continues inward as a plate can be interpreted as a plate undergoing splitting (Fig. 3, *b, c*), but it can also be interpreted as a region with both separate and apposed walls of a fold (Figs. 3, *b, c* and 5, *a, d*). The reason why shallow grooves do not have their walls in apposition is possibly due to the mechanical stiffness of the nuclear membrane (Fig. 4, *a*); a similar tendency for the groove to remain open is exhibited at its fundus (Fig. 3, *a*). Macklin (1916), studying living cells grown in tissue culture continuously for long periods, likewise concluded that apparent partitions extending inward from the nuclear wall are really reduplications of the nuclear membrane, the apposed surfaces being in close contact.

The next point of inquiry concerns the specificity of this type of longitudinal grooving. Although it is common and characteristic of the Brenner tumor and Walthard island, such grooving is not specific to these entities. It can be found also occasionally in the nuclei of connective tissue, smooth muscle, and ordinary epithelium. The fact that the nuclei of the ovarian stromal cells show occasional typical examples gives no convincing support to a stromal origin of these tumors, because the same appearance can also be seen at times in an hypertrophied, cuboidal germinal epithelium of the ovary.

"Wrinkling," with folds extending deep into the interior, is frequently observable in the nuclei of the Sertoli cells of the testis, as has been known from the time of Benda (1887; 1898) and von Bardeleben (1892; 1897); Regaud (1900; 1901) has described this condition fully for the rat. Among textbooks, Maximow and Bloom (1942) state the situation correctly for Sertoli nuclei and illustrate it in 17 out of the 49 nuclei

shown in their Fig. 443. On the other hand, Stieve (1930), in his authoritative work on the male genital system, is misleading in his statement concerning these nuclei: "Gewöhnlich ist die Oberfläche der Kernes ganz glatt, zeight keinerlei Rauhigkeiten, Höcker oder Einbuchtungen." Much the same type of infolded nucleus characterizes the cells of the rete testis, as von Ebner (1902) and Stieve (1930) correctly specify. I have also observed it plentifully in the epithelium of the uterine tube, cervical glands of the uterus and seminal vesicle. Champy and Carleton (1921) claim that furrowed or canalized nuclei are more common than is generally supposed (*cf.* also Guieysse-Pellissier, 1926) and have described occurrences in human and comparative material, including the epidermis, cartilage, sex cells, interstitial cells of the testis, Wolffian duct, nerve cells, enteric epithelium, and lymphocytes. That these authors interpreted some of these examples as localized infoldings (canaliculi) is of no importance. Somewhat similar nuclear appearances have been described for the salivary glands (Garnier, 1900; Guieysse-Pellissier, 1926); gastric glands (Cade, 1901) and epididymis (Henry, 1900). Doubtless many other citations exist in the literature.

The proper explanation of this specialized nuclear configuration is not easy. Five possible explanations at once come to mind: (1) pressure deformation; (2) amitotic activity; (3) nuclear regression; (4) genetic relationship; and (5) surface increase for functional reasons.

1. Pressure Deformation.—Champy and Carleton (1921) have argued with some force that nuclear shape is often due to pressure exerted by various cell inclusions such as fat, yolk, or tonofibrils. The nuclei of cardiac muscle show a pleating of the nuclear membrane, each incision corresponding to a Krause's (Z) membrane. Variations in surface tension at the interfaces of nucleus and cytoplasm may be responsible for nuclei of irregular shape, but this is difficult of proof.

It is true that the cells of a Brenner tumor are crowded and, as they increase, are subject to restraint by the metamorphosis of adjacent ovarian stroma into a fibrous (collagenous) investment. But the cytoplasm is both abundant about these nuclei and is seemingly free from inclusions that might act in the manner Champy and Carleton specify. It is by no means clear how a generalized pressure could result mechanically in longitudinal folding of the Brenner nuclei.

The Sertoli cells are also crowded and their cell bodies are deformed by proliferating sex cells, and especially by the enlarging primary spermatocytes that lie at the level of Sertoli nuclei. In this instance the pressure is specifically against the lateral surfaces of the columnar Sertoli cells, but the nuclei themselves are not directly affected, and again the mechanics of nuclear deformation present difficulties of explanation. Moreover, I have found that the same nuclear shape is seen in the Sertoli cells of cryptorchid testes and in the atrophic seminiferous tubules of old age; in both instances this type of cell is about the only kind seen, and there is no crowding. Neither can generalized pressure explain satisfactorily the abundant occurrence of folded nuclei in the rete testis and many other locations. The suggestion of Champy and Carleton (1921), that nuclear folds or canaliculi may be produced by a mutual cell pressure that inhibits expansion of the nuclear membrane, is not very convincing.

2. Amitosis.—Folded or indented nuclei have long been accepted by some observers as stages illustrative of amitotic nuclear division. This conclusion is largely circumstantial, and, as a generalization, has been viewed with considerable scepticism by many authorities. Lambert (1913) and Lewis and Lewis (1924) have never succeeded in following a single instance of direct cleavage in the nuclei of living cells in tissue culture. In living cells many nuclear constrictions proceed toward apparent completion and then the nucleus returns to its original shape (Macklin; 1916; Lewis and Lewis, 1924).

It has been claimed that mitoses are extremely rare, if not lacking, in cells whose nuclei are incised or canalized (Champy and Carleton, 1921). This would leave amitosis as the only method of cell division open to such cells and invites an interpretation of nuclear incisions as stages in amitosis. Since mitosis has never been reported in a Brenner tumor, an interpretation of amitosis for these atypical nuclei has some theoretical attractiveness despite the unorthodox longitudinal direction of the folding and the occurrence at times of more than one fold (Figs. 1, *m* and 4). Varangot (1938) has subscribed fully to an amitotic ex-

Fig. 4.—Transverse sections of Brenner nuclei, illustrating simple, branched, and double or triple grooves. Camera lucida drawings; ×1500.

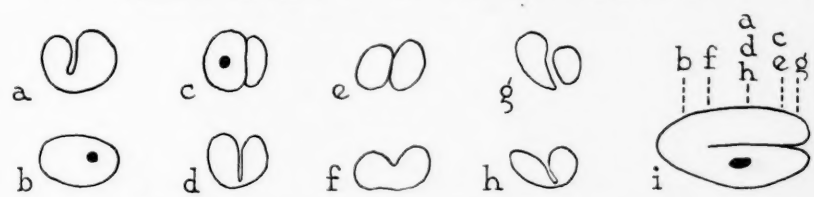

Fig. 5.—Transverse sections of Brenner nuclei. *a, c, e,* and *g,* Focal levels that might be thought to illustrate stages of amitosis. *b, d, f,* and *h,* Deeper focal levels of the same sections that modify the previous judgment. *i,* A nucleus, with the levels of sections *a-h* suggested. Camera lucida drawings; ×1500.

planation for the Brenner tumor nuclei. Regaud (1900), like Bardeleben (1897) and others, originally considered the folded Sertoli nuclei to be undergoing amitosis, but later (1901) he rejected this interpretation, as have Maximow and Bloom (1942). In view of the prevalence of folded nuclei in a Brenner tumor, if amitosis is common there should be adequate and abundant evidence of completely partitioned nuclei and of separate nuclei lying side-by-side within a single cell body. On the contrary, such evidence is lacking. To be sure, instances of cross-sectioned nuclei can be found with two separate or apposed parts. But very many more sections can be found that show discrete nuclear moieties at one focus and joined parts at another focus (Fig. 5, *c-h*). Nuclei are frequently bifid (Fig. 5, *i*), and hence single cross sections that happen to show two nuclear moieties are valueless as critical evidence favoring a binucleate state. It is necessary to insist again, as many have done before, that the mere presence of two nuclei within a single cell body offers no proof of the method by which the binucleate state

was attained. The Brenner tumor is admittedly very slow growing. In view of the infrequency with which mitoses are seen in many faster growing tissues, one should not argue too strongly that amitosis must be the method by which these tumor cells proliferate. Even admitting that amitosis does occur in animal cells, and that it conceivably may be found in a Brenner tumor, it is certain, nevertheless, that amitosis alone cannot explain the prevalence of folded nuclei in this tissue.

3. Nuclear Regression.—Niessing (1888), Tellyesniczky (1897) and La Vallette St. George (1898) have interpreted the folded state of the Sertoli nuclei as stigmas of degeneration, and Stieve (1930) has suggested the same for the nuclei of the rete testis. On the contrary, Benda (1898) and Regaud (1901) do not agree with such an interpretation. If this explanation were correct, one might expect to see similar occurrences in the frankly regressive nuclei of the involuting corpus luteum and in such senescent cells as those of the zona reticularis of the suprarenal gland. Assuming the adequacy of such an explanation, one might then speculate on whether or not the regional variability in the occurrence of folded nuclei in Brenner tumors is indicative of differences in age or functional experience among the cell cords. On the other hand, a regression theory for the Brenner nuclei is seemingly contrary to what can be observed. These cells give no appearance of general retrogression or obsolescence.

4. Genetic Relationship.—It is theoretically possible that the cells of Brenner tumors and Walthard islands are ectopic representatives of cells normally located elsewhere. The similar longitudinal marking of the nuclei of the Sertoli and Brenner cells has impressed Danforth (1942a) who, seemingly unaware of the existence of other examples of this modified nuclear form, alludes guardedly to a possible relationship "which may solve the riddle of the histogenesis of the Walthard rest, the Brenner tumor," etc. Although such a genetic relationship between the Sertoli and Brenner cells may seem to many to be much too speculative to merit serious consideration, yet if any ectopic cell with this nuclear shape is to become suspect, probably the Sertoli cell qualifies best.

The inclusion within the ovary and its adnexa of nongerminal, maleline gonadial cells that later differentiate into specific tumors is, nevertheless, not so simple an hypothesis as at first appears. Numerous perplexing questions arise concerning the prospective potencies of the primitive gonad, its bisexuality, the single (indifferent) or dual (male-female) representation of supporting cells for the gonad, the homology of Sertoli and follicle cells, and the uniqueness of the secondary, definitive ovarian cortex. But some logical difficulties arise even if the possibility of the inclusion of Sertoli-like cells within the ovary and their subsequent differentiation into Brenner tumor cells be assumed. Why, for instance, does an ovarian location (and influence?) lead to a higher frequency of grooving among these cells and a lack of grooving in the rete ovarii cells, when in the male the Sertoli nuclei show less frequent grooving along with abundant, altered nuclei in the cells of the rete testis? In this regard there is no question but that the same primordium becomes either rete testis or rete ovarii, depending upon the swing of sex. The absence of grooving in the nuclei of the rete ovarii (Danforth, 1942a) is astonishing under this hypothesis, since the rete and Sertoli cells in the testis are merely different manifestations of the same basic, nongerminal cell of the gonadial primordium.

The present overwhelming tendency among writers on the Brenner tumor is to attribute the origin of these entities to Walthard cell islands and there let the ancestry rest (Meyer, 1932; Novak and Jones, 1939; and others). This is obviously but one step in the complete identification of antecedents. I should like to suggest here an ultimate origin that is simple and devoid of complications. This is that the common source of both the Walthard islands and the Brenner tumor is the peritoneal epithelium, be it of the serosa of the tube, or other adnexa, or of the specialized germinal epithelium of the ovary. Such a theory does not imply that a Brenner tumor cannot emerge from a Walthard island, but it does urge that it need not do so. In the near future I shall describe in detail a Brenner tumor that connects by a narrow stalk directly with the ovarian epithelium. In this specimen, there is demonstrated for the first time a gradual transformation from the cells characteristic of the germinal epithelium into those of the tumor.

5. *Functional Surface Increase.*—There is a logical and nongenetic way in which many, at least, of the folded or otherwise modified nuclear shapes can be explained. This is that they are direct functional adaptations that arise wherever the proper conditions exist to call them forth. Two kinds of conditions are known to be correlated with nuclei of atypical morphology and increased surface area. One is an unfavorable environment. Macklin (1916) found nuclear fragmentation in old tissue cultures in which the food and oxygen had become depleted and the catabolic products had accumulated, and also in those normal cultures to which a toxic constituent had been added. Similarly Lewis (1911) and Miller and Reed (1912) have demonstrated that the presence of toxins causes an increase in the nuclear lobulation of the neutrophiles in the blood of man, the rabbit, and the guinea pig.

The second condition is active or forced cell metabolism. The nuclei of such cells are frequently not only of large size, but also they gain a marked increase in surface area by the formation of grooves, tubular invaginations, sacculations, lobes, or even complexly branching arms. Extreme forms are encountered in the nurse cells of some eggs and in the spinning glands of various larvae. These correlations are well recognized and may be found summarized in the authoritative reference work of Wilson (1925). Here also is discussed the importance of increased nuclear surface in relation to cell function. Regaud (1901) has traced in detail the occurrence of longitudinally folded nuclei in the Sertoli cells of the rat and has correlated their frequency with the periods of the spermatogenic cycle when the Sertoli cell is presumably most active as a nurse cell to the immature spermatozoa whose heads are buried in it. He found an incidence ranging from zero, or practically so (his Stages 1, 8 to 12), up to 23 or 42 per cent (his Stages 3 to 7). Believing this correlation to be highly significant, he renounced his earlier (1900) interpretation of amitosis to account for such nuclear shapes. Without having verified Regaud's correlation, stage by stage, I can merely add that in an examination of a cryptorchid testis of the rat and of rat testes that had experimentally been made inactive by female hormone administration, the Sertoli cells, which alone constitute the tubule lining, showed grooved nuclei only infrequently. Also in a human cryptorchid and in human testes showing great structural reduction due to advancing age or other causes, the incidence of grooved Sertoli nuclei is seemingly appreciably less than in active testes. Possibly if one were to differentiate stages in human spermatogenesis, as Regaud did for the

rat, the comparison of the extremes of activity and inactivity among Sertoli nuclei would be still more striking.

Passing to the Brenner tumor nuclei, it is possible that the most satisfactory explanation of their modified form (Fig. 4) may be found in one or the other of the conditions just discussed. Of the two, vigorous metabolism has far more support by collateral evidence. If it be objected that definite proof of marked functional activity is lacking, several rejoiners are possible. Present ignorance of the functional role of this relatively new tumor type does not necessarily imply actual functional impotence. Moreover, Marwil and Beaver (1942) have recently described a case (and reviewed some allied instances) in which a Brenner tumor was associated with postmenopausal, uterine bleeding, and other changes usually associated with the presence of estrogens. They have suggested that the tumor might be responsible for the output of ovarian hormone. In this regard one may point out that if the origin of the Brenner tumor should prove to be from the ovarian epithelium, as my critical case seems to indicate, then such an endocrine activity is wholly consistent. The modern trend is to attribute the origin of functional ova and follicles to postpubertal oogenesis from the germinal epithelium (Evans and Swezy, 1931; Everett, 1943). The follicular epithelium is also suspect as the producer of the follicular hormone.

But it would be unwise at present to urge too strongly that the folded nuclear membrane of the Brenner tumor nucleus is correlated with accelerated cellular activity. Too little is known of the general applicability of such an interpretation, since this nuclear form is represented in all the fundamental tissue groups (but only in certain examples of each). In some gland and nurse cells the correlation between nuclear shape and high functional activity is good. In certain other instances of presumably high functional activity, the correlation fails. And in some instances the presence of this nuclear type is both unexpected and puzzling to explain on the basis of an adaptational increase in surface area.

Conclusions

1. The elongated nuclei of Brenner tumors and Walthard cell islands show abundant examples of a longitudinal marking that Varangot first described in 1938 but did not interpret correctly.

2. The nucleus is actually grooved or infolded although the appearance, as viewed, is often more like a longitudinal line or plate.

3. The frequency of occurrence of this modified nucleus varies in different tumor samples and also regionally within the same tumor.

4. Comparable nuclear deformation occurs in various cells in each of the fundamental tissue groups. It is probably commoner than is generally supposed.

5. Longitudinally folded nuclei, of the same type as those of a Brenner tumor, are frequent, for example, in Sertoli cells of the testis and in the epithelium of the rete testis.

6. An explanation of the origin of Brenner tumors and Walthard islands by relating them genetically to indifferent elements of the male type (Sertoli or rete cells), included within the ovary or its adnexa,

can be argued, but not without objection. A simpler explanation that derives the Brenner tumor from the germinal epithelium of the ovary is supported by certain unpublished, direct evidence.

7. Possible explanations of the cause of the longitudinally grooved nucleus are: (a) pressure deformation; (b) amitosis; (c) nuclear regression; (d) genetic relationship; and (e) provision of addition nuclear surface for functional reasons.

8. With respect to the nuclei of Brenner tumor cells, the pressure and amitotic hypotheses are inadequate and unconvincing. General regression, associated with senescence and degeneration, is unproved and apparently contrary to the visible evidence. Genetic relationship furnishes only a proximate and not an ultimate explanation. Increased nuclear surface is a fact, and the most stimulating explanation of this is that an active functional state of the cell is thereby subserved.

9. Although this functional correlation is well established for certain kinds of nuclei with increased surface, it is not known that it holds for all. The extremely high incidence of folded nuclei in a Brenner tumor demands an explanation, but knowledge of the nature and degree of functional activity in this tumor lags.

10. From the foregoing analysis, therefore, one can at present only suggest the possibility of hitherto unsuspected functional potentialities in the Brenner tumor cell. The possibility of estrogenic output requires further attention in view of the author's unpublished evidence of the direct origin of a Brenner tumor from the germinal epithelium of the ovary.

References

v. Bardeleben, K.: Verhandl. d. Anat. Gesell., Versam. **6**: 202, 1892.

v. Bardeleben, K.: Arch. f. Anat. u Physiol., Anat. Abt., Jahrg. (Suppl. Bd.) pp. 193-234, 1897.

Benda, C.: 1887. (Cited by Regaud, 1901.)

Benda, C.: Arch. f. Anat. u. Physiol., Anat. Abt., Jahrg., pp. 385-392, 1898.

Cade, A.: Arch. d'anat. micr. **3**: 1, 1901.

Champy, C., and Carleton, H. M.: Quart. J. Micr. Sc. **65**: 589, 1921.

Danforth, D. N.: Am. J. Obst. & Gynec. **43**: 984, 1942a.

Danforth, D. N.: Am. J. Obst. & Gynec. **44**: 180, 1942b.

v. Ebner, V.: Koelliker's Handbuch der Gewebelehre des Menschen, Aufl. 6, Bd. 3, Englemann, Leipzig, 1902.

Everett, N. B.: Anat. Rec. **82**: 77, 1942; J. Exper. Zool. **92**: 49, 1943.

Evans, H. M., and Swezy, O.: Memoirs Univ. California **9**: 119, 1931.

Garnier, C.: J. de l'anat et de la physiol. **36**: 22, 1900.

Gnassi, A. M.: Am. J. Obst. & Gynec. **33**: 516, 1937.

Grayzel, D. M., and Friedman, H. H.: Am. J. Surg. **53**: 509, 1941.

Guieysse-Pellissier, A.: Arch. d'anat. micr. **22**: 229, 1926.

Henry, A.: Arch. d'anat. micr. **3**: 229, 1900.

Hicks, J. D.: Med. J. Australia **2**: 671, 1941.

Lambert, R. A.: J. Exper. Med. **17**: 499, 1913.

La Vallette St. George, A. J. H.: 1898. (Cited by Regaud, 1901.)

Lewis, F. T.: Proc. Am. Acad. Arts and Sci. **68**: 251-284, 1933.

Lewis, M. R.: Johns Hopkins Hosp. Bull. **22**: 428, 1911.

Lewis, W. H., and Lewis, M. R.: Cowdry's "General Cytology," Sect. 7, University of Chicago Press, Chicago, 1924.

Macklin, C. C.: Carnegie Contr. Embryol. **4**: 69, 1916.

Marwil, T. B., and Beaver, D. C.: Am. J. Obst. & Gynec. **43**: 99, 1921.

Maximow, A., and Bloom, W.: A Textbook of Histology, Philadelphia, 1942, W. B. Saunders Company.
Meyer, R.: Arch. f. Gynäk. **148**: 541, 1932.
Miller, J. A., and Reed, M. A.: Arch. Int. Med. **9**: 609, 1912.
Niessing, C.: Verhandl. d. phys.-med. Gesell. zu Würtzburg. N. F. **22**: Nr. 2, 1888.
Novak, E., and Jones, H. W.: AM. J. OBST. & GYNEC. **38**: 872, 1939.
Plaut, A.: Arch. f. Gynäk. **153**: 97, 1933.
Regaud, C.: Verhandl. d. Anat. Gesell., Versam. **14**: 110, 1900.
Regaud, C.: Arch. d'anat. micr. **4**: 101 and 231, 1901.
Stieve, H.: Ztschr. f. mikr.-anat. Forsch. **10**: 225, 1927.
Stieve, H.: v. Möllendorff's Handbuch der mikroskopischen Anatomie des Menschen, Bd. 7, Teil 2, Berlin, 1930, Julius Springer.
Tellyesniczky, K.: 1897. (Cited by Regaud, 1901.)
Timmerberg, S.: Ztschr. f. Geburtsh. u. Gynäk. **119**: 243, 1939.
Varangot, J.: Gynec. et obst. **38**: 11, 1938.
Wilson, E. B.: The Cell in Development and Heredity, New York, 1925, The Macmillan Company.

A STUDY AND CLASSIFICATION OF NODULAR LESIONS OF THE FALLOPIAN TUBES

"Salpingitis Isthmica Nodosa"

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CHIARI,[1] in 1887, described a condition in which nodular or thickened areas appeared in the Fallopian tubes, chiefly in the isthmic and uterine portions. He pointed out that the nodules, located in the muscular wall of the tube, were made up of nests of glandular tissue which were sometimes connected with the lumen. Chiari named the condition salpingitis isthmica nodosa and believed it to be initiated by an inflammatory process.

The inflammatory concept of etiology has been accepted by most authors and is supported by the frequent association of the nests of epithelium with inflammatory lesions of the salpinx, and by the observation by some authors of beginning epithelization of the cavities of abscesses which have ruptured into the lumen of the tube.[2] Gonococci[3] and tubercle bacilli[4, 5] have been generally accepted as the organisms most frequently responsible for the inflammatory process.

Other theories of etiology have also been advanced. One group of investigators believes the nodules to be due to an abnormal differentiation of the Müllerian apparatus.[6, 7] Another group believes that as the result of developmental defects,[8-10] cells of the mucous membrane of the tubes and uterus are caught in the muscular coats of the salpinx, where they remain dormant and are of no significance unless inflammation ensues.

Some authors[5, 11] conclude that two types of nodularities, due to epithelial nests, can be distinguished. In one type the wall shows epithelial nests which most authors call inclusions, although some investigators[1, 5, 12, 13] have demonstrated that they are connected with the lumen of the tube and with each other. This lesion is generally considered to be the result of inflammatory processes. The other type is due to the extension of endometrium into the wall of the tube and is not associated with inflammation. The weight of opinion suggests that the inclusions of tubal epithelium are more common and that they can readily be distinguished from endometriosis.

The purpose of this paper is to describe the various histologic pictures found in a series of nodular lesions of the tube and to suggest the possible pathogenesis of the conditions. In addition we wish to emphasize that the epithelial nests which appear to be inclusions are, in reality, diverticula.

The literature and controversial issues concerning the pathogenesis of salpingitis nodosa have been summarized by Rabinovitz[13] and Lehwirth.[11]

Materials and Methods

The material for this study was derived from the Fallopian tubes surgically removed from 208 patients treated in the Charity Hospital of Louisiana at New Orleans. Only tubes with gross or microscopic thickening of the wall were selected, and a total of 329 nodules were studied. This number does not represent all of the nodules in the tubes.

Gross and microscopic studies of all of the tubes were made. Intraluminal injections of thorotrast under slight pressure were made into approximately 50 tubes, which were then fixed in formalin and examined roentgenologically. Serial sections were made of twelve nodules.

A cast of the lumen and two of its diverticula was constructed from a segment of the isthmic portion of one tube. This was made by projecting the images, magnified 25 times, of the serial sections of one nodule upon paraffin-beeswax plates of uniform thickness and tracing the outlines of the spaces with a teasing needle. Areas representing the spaces were then cut out and the plates fitted together serially. Plaster of Paris, re-inforced with tie wires and brass rods, was used to make the cast.

Intraluminal injections of a solution of liquid rubber were made of 25 tubes, but the method did not prove satisfactory for our purpose.

Results

Age and Color Incidence.—Of the 208 patients with salpingitis nodosa, 187 were colored and 21 were white, a ratio of 8.9 to 1 (Table I). The largest number of the colored patients (52.9 per cent) was in the fourth decade of life, whereas the largest number of white patients (43.0 per cent) was in the third decade. In the colored group the incidence dropped rather sharply in the decades above and below the fourth; in the white patients a relatively high incidence of the disease was found in the fourth and fifth decades, 23.8 per cent and 28.5 per cent, respectively.

Gross Description of the Lesions.—The majority of the lesions were found in the isthmic portion of the tube, that is, the medial constricted

TABLE I. ANALYSIS OF 208 PATIENTS WITH SALPINGITIS NODOSA ACCORDING TO AGE AND COLOR

AGE RANGE IN YEARS	COLORED		WHITE		TOTAL
	NO.	%	NO.	%	NO.
15-19	6	3.2	1	4.7	7
20-29	47	25.1	9	43.0	56
30-39	99	52.9	5	23.8	104
40-49	30	16.0	6	28.5	36
50-55	4	2.1			4
Unknown	1	0.5			1
Total	187	99.8	21	100.0	208

TABLE II. ANALYSIS OF 329 NODULES OF FALLOPIAN TUBES CLASSIFIED ACCORDING TO TYPES OF LESIONS AND RACIAL INCIDENCE

GROUP		SUBTYPES	COLORED		WHITE		TOTAL	
			NO.	%	NO.	%	NO.	%
I	Diverticulosis	Diverticulosis vera	59	19.9	5	15.1	64	19.4
		Diverticulosis with fibrosis	133	44.9	10	30.3	143	43.5
		Diverticulosis with leucocytic infiltration	26	8.8	9	27.3	35	10.6
		Diverticulosis with intramural abscess	20	6.8	5	15.1	25	7.6
		Diverticulosis with foam cell infiltration	2	0.7	-	-	2	0.6
	Total of Group I		240	81.1	29	87.8	269	81.7
II	Inflammatory lesions without diverticulosis	Intramural fibrosis	20	6.8	1	3.0	21	6.4
		Intramural abscess	5	1.7	1	3.0	6	1.8
		Tuberculosis	4	1.3	1	3.0	5	1.5
		Intramural foam cell infiltration	2	0.7	-	-	2	0.6
		Intramural cholesteatoma	2	0.7	-	-	2	0.6
		Intramural leucocytic infiltration	1	0.3	-	-	1	0.3
	Total of Group II		34	11.5	3	9.0	37	11.2
III	Endometriosis		21	7.1	1	3.0	22	6.7
IV	Intramural carcinoma		1	0.3			1	0.3
	Total of all groups		296	100.0	33	99.8	329	99.9

third.[14] Large nodules were found almost exclusively in this area; smaller lesions were occasionally found in the ampullary portion.

Some of the nodules were distinct, rounded masses which involved a single portion of the wall. The majority, however, were represented by focal, fusiform swellings which involved the entire circumference of the tube and frequently were demonstrated better by palpation than by inspection. The nodules were usually firm or hard in consistency, and presented smooth, regular surfaces, although occasionally larger nodules showed surface irregularities. The serosal surface was smooth and rarely showed local adhesions. When adhesions were observed, they usually were part of a generalized pelvic inflammation and did not seem to have originated in the region of the nodules.

The color of most nodules was not different from that of the adjacent, nonnodular portion of the tube. Some of the larger nodules, however, were pale or even translucent, and some were yellowish white or brownish yellow.

Many of the lesions were multiple, and in the tubes which were extensively involved, the wall often had a beaded appearance. Counts of the number of lesions present, as indicated by palpation and inspection, were frequently proved inaccurate by later roentgenologic studies, which almost invariably increased the number counted.

Some nodules measured as much as 2.5 cm. in diameter. In other cases, the thickening was so slight that its presence could be definitely established only by microscopic examination. Even though no focal

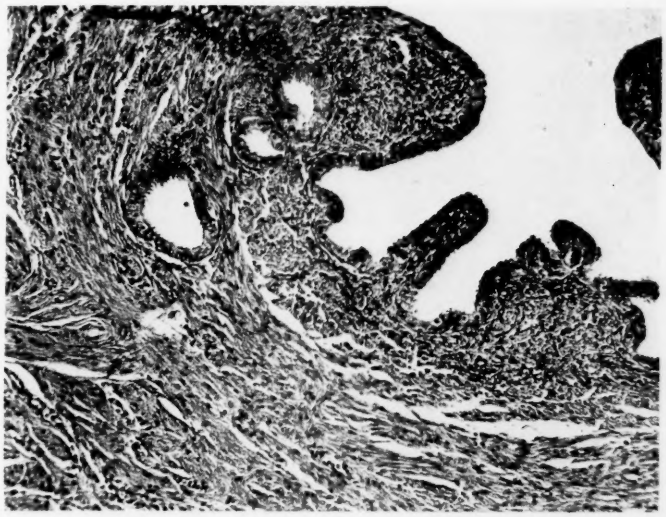

Fig. 1.—Cross section through the isthmus of a Fallopian tube showing an early lesion of diverticulosis. Note the spaces, lined by ciliated columnar epithelium, in the muscle coat directly beneath the mucosa. Hematoxylin and eosin; ×108.

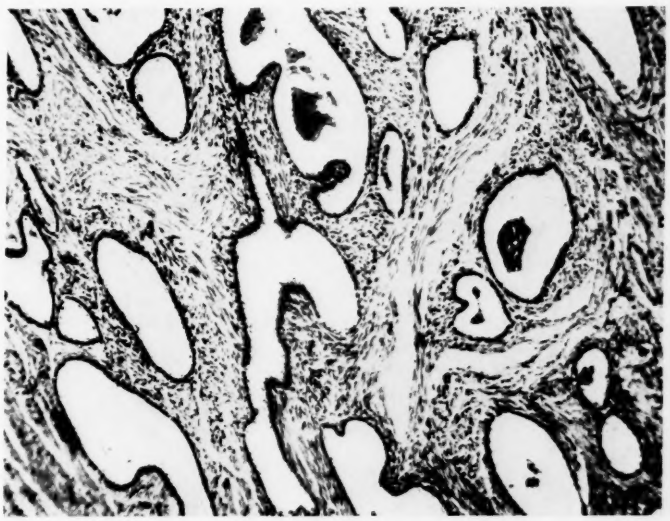

Fig. 2.—Cross section through the isthmus of a Fallopian tube showing diverticulosis vera. Note the irregular epithelial-lined spaces lying between the muscle fibers of the wall of the tube. Hematoxylin and eosin; ×100.

thickening could be seen or palpated, very early lesions were frequently found in the routine microscopic sections of the isthmus of tubes which showed other evidences of inflammation.

Classification of the Lesions.—The lesions were classified into four major groups (Table II). Groups I and II were subdivided because of the differences in the cytologic factors which accounted for the nodularity.

Group I. Diverticulosis (81.7 per cent).—Before the various subtypes are described, a general description of diverticulosis will be presented.

Collections of simple columnar or pseudostratified epithelium, arranged to form irregular alveolar spaces, were included in the muscular coat of the tube (Figs. 1 and 2). In most instances the cells were indistinguishable from those of the tubal mucosa; some were ciliated. The larger spaces were often lined by somewhat flattened cuboidal epithelium.

Fig. 3.—Roentgenogram of a Fallopian tube injected with thorotrast. The diverticula responsible for the nodule are in the isthmus at the right. Note the variation in size and shape of the spaces.

The character of the inclusions of epithelium varied. Sometimes the alveoli were collected in small multiple foci, each of which was separated by a distinct mass of muscle fibers. In other cases there were innumerable epithelial-lined spaces scattered uniformly throughout the muscle wall, from the mucosa to the serosa, and separated from each other by only a small amount of muscle tissue. In this type of lesion the entire wall was converted into a honeycomb of spaces in which the lumen of the tube could sometimes be identified only by a regular circular arrangement of the muscle around it.

The alveolar spaces varied both in shape and size. Generally speaking, the smaller spaces were irregularly rounded; the larger ones frequently assumed irregular shapes, with angularities and bulbous dilated areas. Some spaces had slitlike lumina; others, which were markedly dilated and cystic, measured as much as 0.4 cm. in diameter.

Often the spaces were completely empty. Sometimes they contained a homogeneous or a granular coagulum. Other spaces were filled with either desquamated epithelial cells or macrophages with or without phagocytosed brown pigment. Very occasionally a purulent exudate filled the lumen.

Hypertrophy of the muscle tissue was observed, although the degree and frequency of this change, as related to the extent of epithelial invasion, was difficult to determine.

The true nature of these spaces was not evident until they were visualized with x-ray following the instillation of thorotrast into the lumen of the tube. The roentgenograms (Fig. 3) confirmed the variations in the size, shape, number, and distribution of the diverticula observed in single paraffin sections. In some films only a few small, budlike outpouchings from the lumen were observed. In others the maze of opaque channels in the wall of the tube was so great that the lumen of the tube was almost completely obscured (Fig. 4). Often the lumen was narrowed in the area of the diverticulosis, and occasionally was completely occluded distal to it (Figs. 5 and 6).

Fig. 4.—Roentgenogram of a Fallopian tube injected with thorotrast. Grossly, the isthmus was markedly thickened and nodular. The diverticula are so numerous that the lumen is only faintly visible as it passes through the nodule.

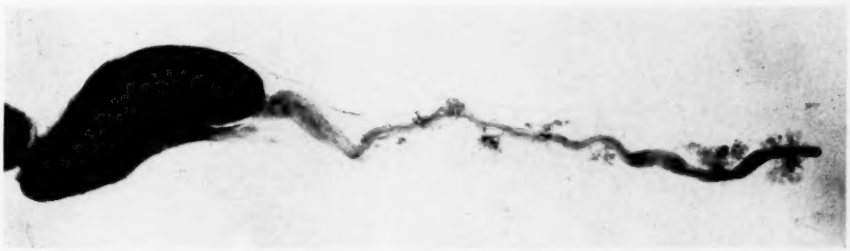

Fig. 5.—Roentgenogram of a Fallopian tube injected with thorotrast. The isthmus shows numerous diverticula, some of which were not evident grossly. The lumen of the tube is occluded medial to the last nodule on the right. The plaster of Paris cast was constructed from this nodule.

Single and serial paraffin sections, made from the tubes injected with thorotrast, showed the granular brownish precipitate of the opaque substance in the lumen of the tube and in the majority of the epithelial-lined spaces in the wall. Scattered spaces, however, remained unfilled.

Serial sections of the tubes thus studied confirmed the x-ray findings and showed that the spaces were part of a complicated intercommunicating network making up one or more diverticula.

The plaster of Paris cast (Fig. 7) prepared from serial sections of two diverticula in one tube, also confirmed the x-ray studies. Each of the diverticula was attached to the lumen of the tube by a single rather broad connection. Beyond these attachments a complicated anastomosing network of tubules ramified through the wall of the tube. The long axis of these tubules was, in general, parallel to the long axis

of the lumen of the tube. Small collections of tubules were unconnected with the lumen.

The subtypes were classified as follows:

1. *Diverticulosis Vera (19.4 per cent) (Fig. 2).*—In this lesion, diverticula were solely responsible for the nodularity, although in some instances the connective tissue and muscle directly beneath the mucosa was infiltrated with a few inflammatory cells.

2. *Diverticulosis With Fibrosis (43.5 per cent).*—In addition to diverticula, fibrosis of the muscularis of the tube was observed in this lesion. In many instances a few chronic inflammatory cells were also present. The relative proportions of diverticulosis and fibrosis varied greatly. It was apparent in all instances that the fibrosis contributed to the nodularity.

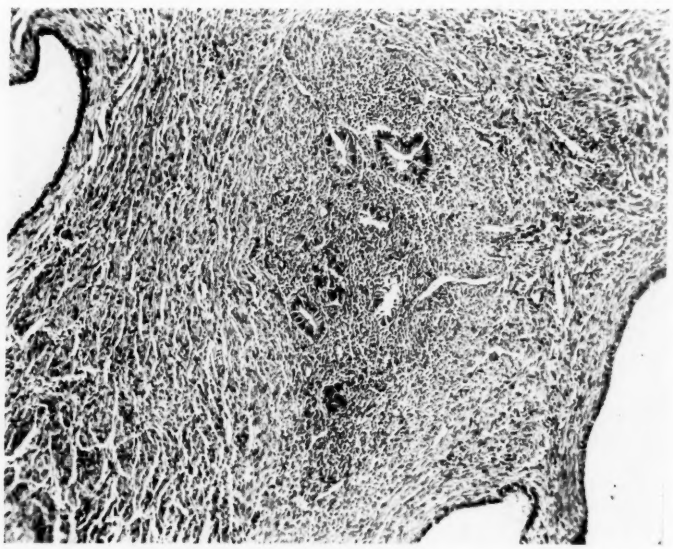

Fig. 6.—Cross section through the isthmus of a Fallopian tube at the point of occlusion of the lumen. Note the remnants of the mucosa embedded in scar tissue infiltrated with lymphocytes. Portions of diverticula are represented by the large epithelial-lined spaces which lie in the muscle coat.

3. *Diverticulosis With Leucocytic Infiltration (10.6 per cent).*—In this lesion diverticulosis was accompanied by leucocytic infiltration of the wall of the tube. Slight fibrosis of the muscularis was usually present. The relative proportions of diverticulosis and leucocytic infiltration varied greatly. Most of the inflammatory cells were lymphocytes which were diffusely scattered or distributed in a focal manner. Lymph follicles with well-developed germinal centers were occasionally noted in the dense cellular infiltrations which frequently appeared beneath the mucosa. Macrophages were not infrequently present in the form of foam cells. Plasma cells, eosinophiles and neutrophiles were occasionally noted.

4. *Diverticulosis With Intramural Abscess (7.6 per cent) (Fig. 8).*—Chronic intramural abscess was the most prominent feature of this lesion. Spaces lined with epithelium often were not numerous, and in some lesions only fragments of epithelium were present in the abscesses.

Single or multiple abscesses were present in single nodules, and the shape of some of the larger abscesses suggested that they had been formed by the coalescence of smaller single abscesses. Our material did not show an abscess draining into the lumen of the tube, such as other observers have described.

5. *Diverticulosis With Foam Cell Infiltration (0.6 per cent).*—In this lesion the wall of the tube showed large focal accumulations of foam cells in addition to the diverticula.

Fig. 7.—Plaster of Paris cast of one nodule in the isthmus of a tube. The lumen of the tube is represented by the central large solid shaft. Two diverticula are present, one on either side of the lumen. Each communicates at right angles with the lumen at the sites of the arrows. Note the variation in size and shape of the intercommunicating tubules. In general, the long axis of each tubule runs parallel to the long axis of the lumen. Some tubules do not communicate either with other tubules or with the lumen. Those at the lower right are from another diverticulum. ×25.

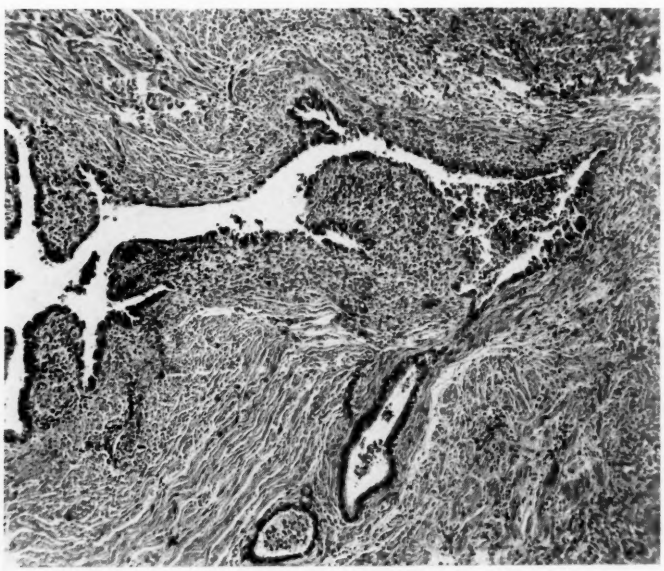

Fig. 8.—Cross section through the isthmus of a Fallopian tube showing diverticulosis and intramural abscess. The diverticulum arises from the lumen of the tube at the left. The edge of the abscess wall is at the upper right. Hematoxylin and eosin; ×108.

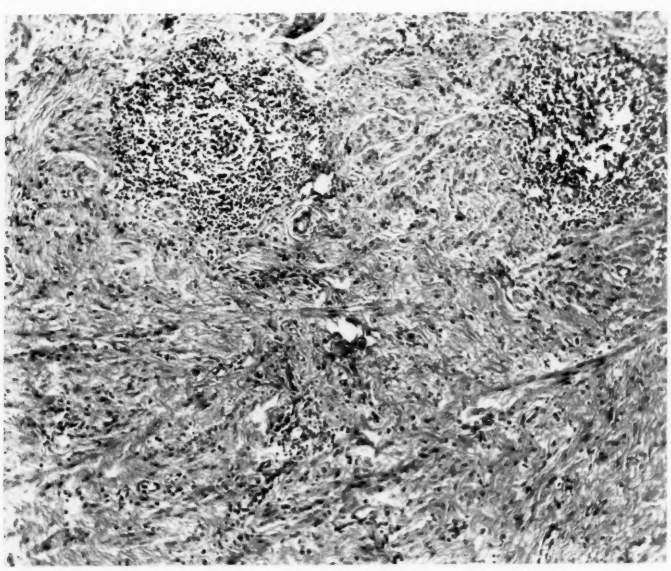

Fig. 9.—Cross section through the isthmus of a Fallopian tube showing intramural fibrosis. Most of the muscle is replaced by scar tissue. Lymph follicles are present. Hematoxylin and eosin; ×125.

Group II. Inflammatory Lesions Without Diverticulosis (11.2 per cent).—1. *Intramural Fibrosis (6.4 per cent) (Fig. 9):* All degrees of scarring of the muscle, plus a mild degree of chronic inflammation, were noted. Occasionally foci of lymphocytes were present. This lesion apparently represented the end stage of an inflammatory process.

2. *Intramural Abscess (1.8 per cent):* These lesions resembled those described in diverticulosis with intramural abscess except for the absence of epithelial-lined spaces.

3. *Tuberculosis (1.5 per cent):* These lesions presented the usual histologic picture of tuberculosis.

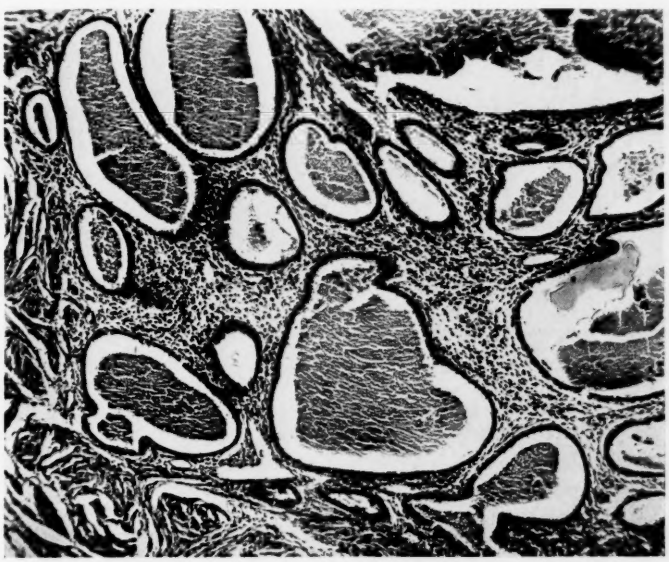

Fig. 10.—Cross section through the isthmus of a Fallopian tube showing endometriosis. Note the typical endometrial stroma and glands. The granular material in the lumina of the glands is thorotrast. Hematoxylin and eosin; ×75.

4. *Intramural Foam Cell Infiltration (0.6 per cent):* This lesion was found in two cases. One case showed a widespread, diffuse macrophagic infiltration of almost the entire wall of the tube. Most of the macrophages were of the foam cell type. The other case showed large focal accumulations of foam cells about a small focus of necrotic tissue in the wall of the tube.

5. *Intramural Cholesteatoma (0.6 per cent):* This lesion consisted of a collection of granular necrotic amorphous material in which many cholesterol clefts were present. There was a zone of mild chronic inflammatory reaction about the necrotic material.

6. *Intramural Leucocytic Infiltration (0.3 per cent):* This lesion was characterized by marked diffuse infiltration of the wall with round cells, most of which were lymphocytes. No necrosis and very little fibrosis were present.

7. *Lymphogranuloma Venereum:* A case in which lymphogranuloma inguinale was identified as the cause of tubal nodularity has previously been reported[15] and is not included in this series.

Group III. Endometriosis (6.7 per cent).—Glands similar to uterine glands and a stroma indistinguishable from endometrial stroma were

present in the wall of the tube (Fig. 10). All lesions in this group were located in the isthmic portion of the tube, and most of them were very near the uterine portion. In some cases morphologic variations compatible with the cyclic changes observed in normal endometrium were found in both the glands and stroma. One tube in this group was studied roentgenologically. It presented a communication between the glandular spaces of the nodule and the lumen of the tube.

Group IV. Intramural Carcinoma (0.3 per cent).—This lesion was a metastatic carcinoma of the endometrium. The nodule consisted of an isolated mass of neoplastic cells in the wall of the isthmic portion of the tube.

Comment

Diverticula, alone or in association with acute or chronic inflammatory lesions, accounted for 81.7 per cent of the nodules. Even though all of the epithelial "inclusions" which were observed on microscopic examination were not proved to be diverticula by x-ray or serial section, we feel justified in classifying them as such because of the consistency of this finding in those tubes which were examined by these methods. Less frequent causes were inflammatory lesions alone, endometriosis, and metastatic carcinoma.

The disproportionately high incidence of the various forms of diverticulosis and of inflammatory lesions with diverticulosis in colored as compared to white women was a true disproportion. During a ten-year period, of which the period included in this investigation was a part, the ratio of white to colored gynecologic admissions to Charity Hospital was approximately 1 to 1[16] (52.01 per cent to 47.99 per cent, respectively), whereas the proportion of white to colored cases of tubal nodularity was approximately 1 to 9.

One reason for the preponderance of these types of lesions in the colored race is that the colored females admitted to the Charity Hospital gynecology service frequently have gonorrheal salpingitis, a disease which is closely related to nodular lesions of the tube. Another reason is that more tubes were removed from colored than from white patients because colored women have leiomyomas of the uterus approximately eight times more often than do white women,[16] and salpingectomy is often done in combination with hysterectomy for this condition.

The highest incidence of tubal nodularity in white women was in the third decade, and that of colored women was in the fourth decade of life (Table I). The explanation of this lies in the fact that many of the tubes from the colored patients had been removed not because of tubal disease, but during the course of a hysterectomy for uterine leiomyomas, a disease which commonly manifests itself in the Negro during the fourth decade of life.[16] On the other hand, many of the tubes from white patients were removed because of primary tubal disease, which manifests itself at an earlier age. That these conditions were factors in the age distribution is supported by the fact that diverticulosis in

the colored race was frequently accompanied by fibrosis, indicating that the lesions were of long duration, whereas diverticulosis in the white race was frequently associated with suppurative inflammatory lesions, indicating that the lesions were of more recent origin. The age incidence, therefore, seemed to depend more on the circumstances which permitted us to examine the tubes than on any fundamental difference in the disease process in the two races.

The pathogenesis of the most common lesion, diverticulosis, is of great interest. The frequent association of inflammatory processes with the diverticula seems to leave little doubt that inflammation is an etiologically related lesion. This thesis is supported by the observations of other workers, who have described epithelization of the cavities of abscesses which have ruptured into the lumen of the tube. It is also possible that deep ulcers of the mucosal surface may allow the epithelium to gain access to the muscular coat. From an anatomic standpoint the absence of a muscularis mucosa in the Fallopian tube makes the muscular coat more readily accessible to invasion by the tubal epithelium.

Once the epithelium is established in the muscular coat, whatever the means of invasion may be, it apparently proliferates slowly and invades the muscular tissue widely. The proliferation of the epithelium may be accounted for in large part by nonspecific stimuli arising in association with the reparative and regenerative processes which occur in chronically inflamed tissue. In addition, muscular contractions of the tube may tend mechanically to push the acini between the muscle fibers. It is possible, finally, that cyclic hormonal influences may cause proliferation of the epithelium; invasion of the muscular coat of the uterus by uterine glands has been described in mice receiving large doses of estrogens.[17]

Whatever the exact mechanism of pathogenesis may be, it is interesting to note that similar epithelial invasions are found in the muscular wall of the chronically inflamed gall bladder, the anatomic structure of which is similar to that of the Fallopian tubes.

Summary

1. Three hundred and twenty-nine nodules in the walls of Fallopian tubes of two hundred and eight patients were studied.

2. Eighty-one and seven-tenths per cent of the nodules were due to diverticula of tubal epithelium alone or in association with acute or chronic inflammatory lesions. We have suggested the term diverticulosis of the Fallopian tubes for these types of lesions.

3. Eleven and two-tenths per cent of the nodules were due to inflammatory lesions without diverticulosis; six and seven-tenths per cent were due to endometriosis and three-tenths per cent were due to metastatic carcinoma of the endometrium.

We are indebted to Drs. Robert Rose, Norman C. Woody and Charles Wise, who prepared the cast of the Fallopian tube while they were fourth year students in the School of Medicine at Louisiana State University.

References

1. Chiari, H.: Cited by Lehwirth, S.[11]
2. Fogel, I.: Monatschr. f. Geburtsh. Gynäk. **77**: 221, 1927.
3. Schautta: Cited by Lehwirth, S.[11]
4. Bulius: Deutsche med. Wchnschr. **35**: 1293, 1909.
5. Frankl, O.: Arch. f. Gynäk. **135**: 556, 1929.
6. v. Recklinghausen: Cited by Rabinovitz, M.[13]
7. Schridde, H., and Schonholz, L.: Cited by Frankl, O.[5]
8. Rosenberger, M.: Arch. f. Gynäk. **114**: 601, 1921.
9. Lahm, W.: Zentralbl. f. Gynäk. **45**: 133, 1921.
10. Babes, A.: Gynécologie **26**: 400, 1927.
11. Lehwirth, S.: Zentralbl. f. Gynäk. **60**: 1110, 1936.
12. Maresch, R.: Cited by Rabinovitz, M.[13]
13. Rabinovitz, M.: Am. J. Obst. **68**: 711, 1913.
14. Gray, H.: Anatomy of the Human Body, ed. 20, Philadelphia, 1918, Lea & Febiger, p. 1257.
15. D'Aunoy, R., and Schenken, J. R.: J. A. M. A. **110**: 799, 1938.
16. Levy, W. E.: Tri-State M. J. **13**: 2692, 1941.
17. Loeb, L., Suntzeff, V., Burns, E. L.: Am. J. Cancer **34**: 413, 1938.

FETAL TACHYCARDIA DURING LABOR*

A Fallible Sign of Fetal Distress

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MOST obstetricians believe that an unusually rapid fetal heart rate is a sign of distress in the infant. Rates of 160 beats or more per minute are considered with anxiety, whereas rates between 180 and 200 are considered with alarm. Because of this fear it is common practice to deliver these infants, usually by some hazardous operative procedure, as quickly as possible. Babies born of such labors are sometimes asphyxiated, sometimes injured, and sometimes dead. It is reasonable to suppose that the distress of many of these fetuses takes place at the time of delivery and not at the time of the tachycardia.

This report deals with a group of infants that survived periods of tachycardia without specific treatment and without evidence of asphyxia or injury at birth.

Of historic interest is von Winckel's[1] report of 1903, as he was one of the first to advise immediate delivery of a fetus whose heart rate exceeded 160. This policy was widely accepted and has become a principle of obstetric teaching. The universal appeal of a mathematical method for medical practice probably contributed toward the perpetuation of this teaching.

*Aided by a grant from the Wisconsin Alumni Research Foundation.

The research of Baumm[2] corroborated von Winckel's opinion. Baumm considered fetal tachycardia during labor as most dangerous and almost certainly indicative of intracranial hemorrhage. He even went so far as to state that efforts of delivery were useless once tachycardia had appeared. These opinions were made after autopsy of 11 infants had revealed intracranial hemorrhage, and after obstetric records had indicated tachycardia during labor. The report also stated that most of the labors were arduous and that 2 of the 11 were terminated by difficult forceps delivery. His conclusion that a fetal heart rate which increased to 160 or 170 during labor was indicative of intracranial hemorrhage seems unjustified.

One of the first to disagree was Bartholomew[3] who, in 1925, said that rapid rates were not serious and moreover that they were infrequently observed. Freed[4] found 8 fetuses with tachycardia in 500 labors; no more than two of the 8 infants were asphyxiated. Richardson[5] was able to predict impending fetal distress due to separation of one-fourth to one-half of the placenta by an acceleration of the fetal heart rate; if further separation took place, the tachycardia was replaced by bradycardia. Rates from 160 to 180 were not regarded seriously by King,[6] and those over 180 were not considered dangerous unless accompanied by strong uterine contractions.

Baumm[2] was aware of the frequency of rapid fetal heart rates during pregnancy and early labor and considered them to be unimportant, a contrast to his belief about tachycardia during active labor. Recent studies by Sontag and Newberry[7] indicate that three-fourths of all patients have fetal heart rates of 160 or over without evidence of fetal distress at some time during the last two months of pregnancy.

Custom has given a figure of 160 as the upper limit of a normal fetal heart rate. I shall continue this usage to the extent that all rates over 160 are considered rapid, but this abnormality need not imply distress or danger. For convenience, two artificial classes have been created, transient fetal tachycardia and persistent fetal tachycardia. An arbitrary time limit of twenty minutes separates the two classes. Experienced observation soon reveals that transitory tachycardia is common, persistent tachycardia uncommon. Henceforth in this publication a transient fetal tachycardia indicates a rate of 160 or more beats per minute obtained by a count of thirty seconds but with a duration of less than twenty minutes, whereas a persistent tachycardia indicates that the rate exceeded 160 for twenty minutes or longer. An increase of this arbitrary period of time from twenty to thirty minutes or a reduction of the period to fifteen minutes would have resulted in small and unimportant changes in the proportions of transient and persistent fetal tachycardia.

Methods and Material

Data were obtained by extensive observations of 250 women throughout labor. The findings were considered adequate only when the study began early in labor, when the rate was observed frequently during early labor and continuously during the late first stage and second stage of labor, when the rate was calculated from graphic records as well as

by auscultation and when the recorded rate was obtained at the end of the interval between contractions. Observations which failed to meet these standards were considered inadequate and were excluded.

It must be noted that gross inaccuracies are common when rates faster than 175 beats per minute are counted by auscultation. Extensive experience and the use of a stop watch may be combined to improve the accuracy of counting, but rates obtained by use of an ordinary watch for short intervals of time are worthless for research purposes. Accurate graphic recording of the rate obviates most difficulties, hence in these studies recordings were made with the Endocardiograph. This is a device which produces a phonocardiogram.[8]

Results

Incidence.—Of the 250 patients studied 58 exhibited fetal heart rates in excess of 160 (Table I). Table I shows the infrequency of persistent tachycardia, and it should also be noted that rates above 180 are rarely observed. On two occasions only have rates above 190 been recorded; one was 210 and one was 214 (Fig. 1). Further analysis of incidence according to period of labor indicates that seven of the persistent class

TABLE I. INCIDENCE OF FETAL TACHYCARDIA IN 250 DELIVERIES

	NO. OF CASES	PER CENT
Persistent* (Maintained for 20 min.)		
Rate above 160	6	2.4
Rate above 170	5	2.0
Rate above 180	3	1.2
Rate above 190	0	
Total	14	5.6
Transient (Not maintained 20 min.*)		
Maximum rate between 160-169	29	11.6
Maximum rate between 170-179	9	3.6
Maximum rate between 180-189	6	2.4
Maximum rate over 190	0	
Total	44	17.6
Grand Total	58	23.2

*Rates may have been higher for a short time but never lower. Thus, two infants exhibiting rates of 210 and 214 were included in this group.

and 20 of the transient class were found in early labor, a frequency of approximately 50 per cent. Six alone (Figs. 2 and 6) of the persistent class and two of the transient class had rates in excess of 160 at the last observation possible, which was a minute or two before delivery. The remainder of the rapid rates were observed at a time between the period of early labor and delivery.

Asphyxia.—Our criteria of asphyxia are stringent and have been stated elsewhere.[9] Briefly, mild asphyxia indicates that spontaneous respirations are delayed more than a minute after birth and without signs of oxygen want; moderate asphyxia indicates apnea, cyanosis and need of resuscitative methods while severe asphyxia indicates apnea, shock, severe oxygen want, and prolonged need of resuscitative methods.

Of the 14 classified as persistent fetal tachycardia, 12 breathed spontaneously within thirty seconds after delivery, one breathed spontaneously within ninety seconds and was called mildly asphyxiated. This mildly asphyxiated infant was a first born weighing 10½ pounds; a delay of five minutes was incurred during delivery of the shoulders

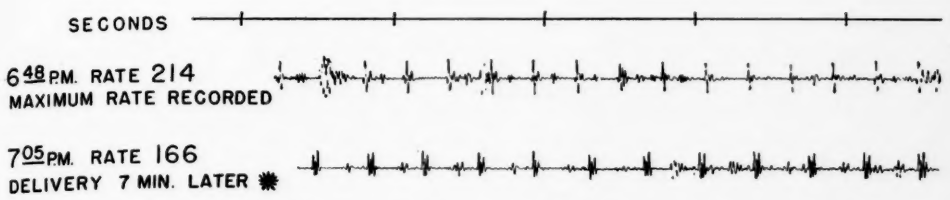

Fig. 1.—The most rapid rate recorded. Note that the rate decreased spontaneously to 166. There was no evidence of fetal distress or neonatal asphyxia at birth.

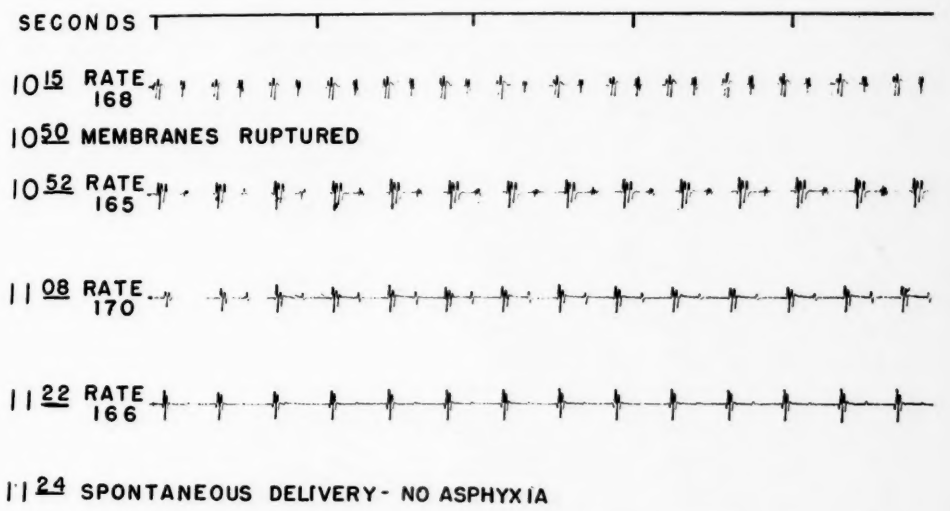
SECONDS
10 15 RATE 168
10 50 MEMBRANES RUPTURED
10 52 RATE 165
11 08 RATE 170
11 22 RATE 166
11 24 SPONTANEOUS DELIVERY - NO ASPHYXIA

Fig. 2.—This record illustrates untreated persistent fetal tachycardia. The infant was normal at birth although the heart rate had exceeded 160 for sixty-nine minutes before delivery.

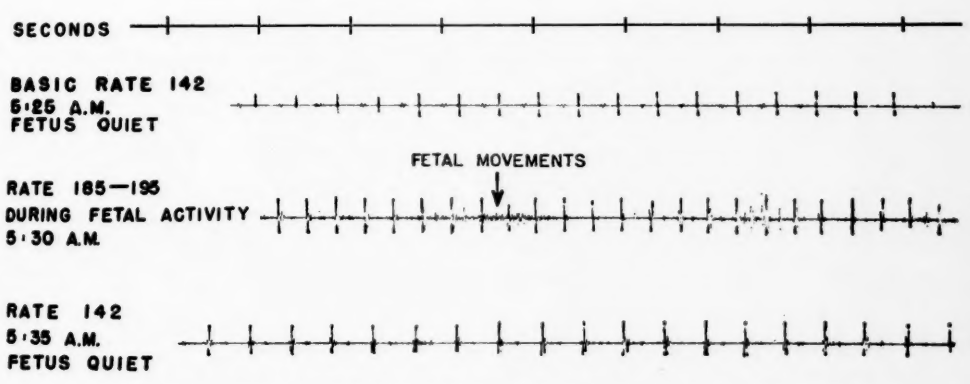

Fig. 3.—Fetal activity was followed by tachycardia, then the rate returned to normal during quiescence. Note that the fetal movements were clearly recorded during the period of activity. This record was made early in labor.

because of dystocia. One infant, presenting by breech, was delivered by craniotomy after it had died during delivery because of cephalopelvic disproportion. This death was unrelated to the tachycardia and shall be excluded from further consideration.

Two moderately asphyxiated infants were delivered from the group of 44 classified as transient fetal tachycardia. One was born by a difficult forceps delivery and the other was depressed because the mother had received 7½ gr. of pentobarbital sodium as an hypnotic agent during labor. There were no severely asphyxiated infants.

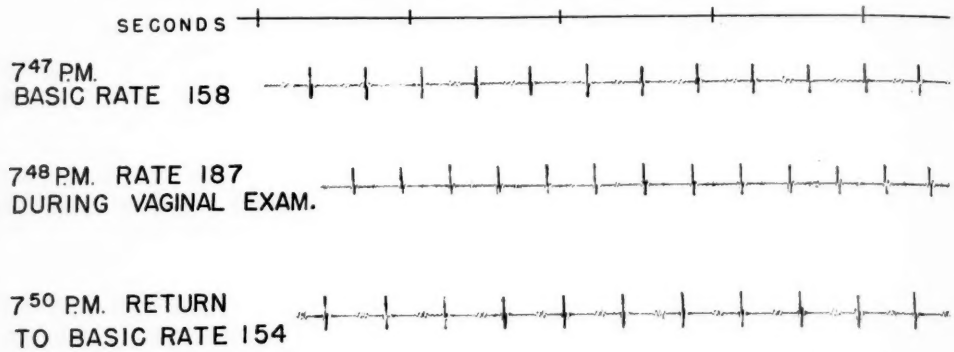

Fig. 4.—Record shows fetal tachycardia occurring during vaginal examination in the second stage of labor. The transient acceleration was associated with palpation of the fetal head. This procedure may also produce a temporary slowing of the fetal heart rate.

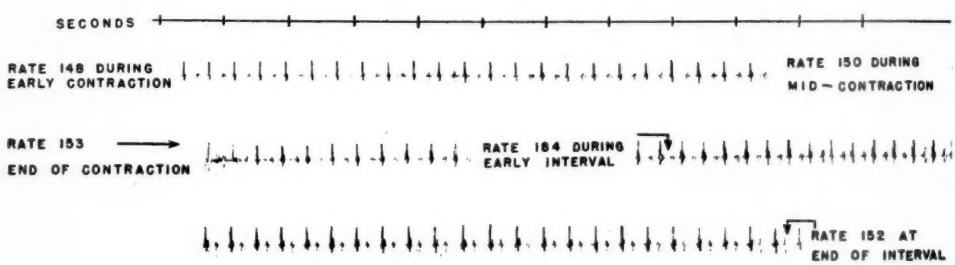

Fig. 5.—The rate was stable at about 150 during the entire contraction but quickly accelerated to 184 in the early interval. A gradual slowing brought the rate again to normal during the interval. Tachycardia immediately after a contraction is unusual.

Returning for the moment to those infants of both classes who had tachycardia just before delivery, the data indicate that one was mildly asphyxiated, the five others were normal. The circumstances of this mild asphyxia were told in a preceding paragraph.

Death.—There was but a single death, a stillbirth which was delivered by craniotomy. There were no neonatal deaths.

Etiologic Factors.—To determine the cause of fetal tachycardia has not been the purpose of this report, yet careful study of the state of labor at the time of tachycardia gives data worthy of record and thought. Table II lists the likely causes of transient fetal tachycardia. No cause was found for half of these rapid heart rates. Of the remainder most were due either to fetal activity or to pressure on the fetal head (Figs. 3, 4, and 5).

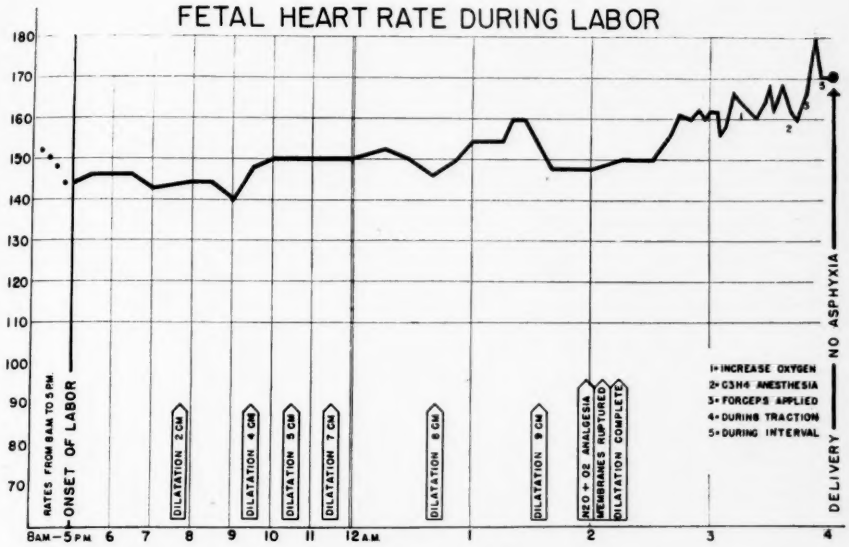

Fig. 6.—Graph of fetal heart rate throughout labor. The tachycardia appeared late in labor without apparent cause and persisted for over an hour. Administration of oxygen was without effect. Note that there was an additional increase in rate when forceps were applied. The infant was born without asphyxia.

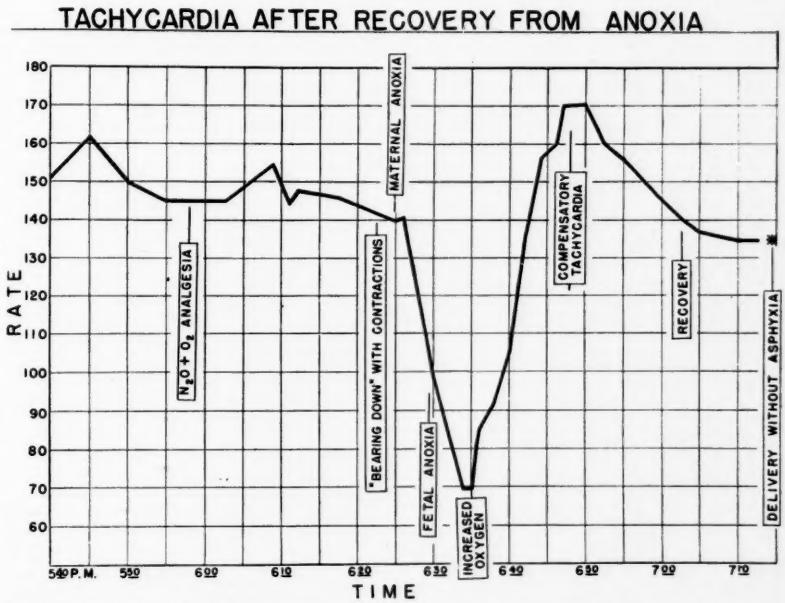

Fig. 7.—In this patient anoxia produced a slow fetal heart rate without evidence of a preliminary tachycardia. Administration of oxygen to the mother quickly corrected the fetal bradycardia. The succeeding compensatory tachycardia gave way to a normal rate after a few minutes.

TABLE II. FACTORS CONCERNING THE ETIOLOGY OF TRANSIENT TACHYCARDIA

Fetal movements and activity	5 cases
Application of forceps	2 cases
Pressure of fetal head against perineum	7 cases
Uterine contractions	6 cases
Stimulation from rectal or vaginal examinations	2 cases
Unexplained	22 cases
Total	44 cases

It is apparent that fetal activity, application of forceps and vaginal examination played little part in the etiology of persistent tachycardia, because these factors did not persist for twenty or more minutes. It is difficult to determine any cause for the persistent class (Fig. 6). Nine of the 14 infants of this class developed tachycardia after the membranes had ruptured. In three infants only was the umbilical cord around the neck. There were a few other less likely factors but discussion of such minor details would be fatuous.

Thus far anoxia has been deliberately omitted from the discussion of etiologic factors. There was clinical evidence of anoxia in eight of the women. In only one of these individuals was the fetal tachycardia noted at the time of anoxia. In another infant the anoxia appeared long after the tachycardia and was wholly unrelated. In the six remaining, anoxia resulted in fetal bradycardia, the usual reaction.[8] However, after oxygen was administered to the mother, the fetal heart rate returned to normal but then continued to accelerate and reached levels above 160 where the rate persisted for varying periods of time (Fig. 7). Continued administration of large amounts of oxygen to the mother was without effect on the fetal heart rate. Notwithstanding many attempts, at no time was it possible to reduce a rapid fetal heart rate by administration of oxygen to the mother.

Discussion

The frequency of transient fetal tachycardia contrasts with the infrequency of persistent fetal tachycardia; in this study the ratio was approximately 3:1. Sontag[7] reported an incidence of from 72 to 76 per cent of fetal tachycardia at some time during the last two months of pregnancy. The discrepancy between Sontag's and these figures may be explained by two factors. First, there is a definite tendency for the fetal heart to beat more slowly after active labor is established.[10] It is well to remember that half of our instances of tachycardia appeared early in labor. Second, I have attempted to record the basic fetal heart rate at all times; a basic rate is obtained at the end of the interval between uterine contractions and at a time when the infant is not unusually active. Continuous auscultation during the early course of labor, no doubt, would have disclosed additional instances of transient fetal tachycardia. Although these observations indicate that fetal tachycardia may occur in 25 per cent of the patients during labor; in most instances the rapid heart rate does not persist for twenty minutes. Furthermore, fetal heart rates above 200 are very rare and in my experience have always been transient.

However great or small the incidence of fetal tachycardia, it is of academic interest alone so long as the fetus remains free from danger. As there was but a single death in this group of infants, a death from causes definitely apart from the tachycardia, no little doubt is raised about the hazards usually attributed to rapid fetal heart rates. Neither was there danger in the form of neonatal asphyxia, as this was found in three infants only. While fetal tachycardia might have been a sign of impending asphyxia in these three infants it is unlikely because on two occasions dystocia influenced the fetus *after* the period of tachycardia and in the remaining instance the fetus was depressed by an hypnotic drug. No infant had neonatal complications which could be ascribed to fetal distress in utero.

Clinical observations do not permit speculation about the physiologic mechanism of fetal tachycardia. Windle[11] has summarized excellently the meager physiologic data now available. Baumm[2] was one of the first to report that active fetal movements during pregnancy were followed frequently by an acceleration of the fetal heart rate, an observation recently elaborated by Sontag.[12] Such tachycardia occurs not only during pregnancy but also during labor; however, active fetal movements usually decrease as labor progresses and consequently tachycardia from such a cause is less common late in labor.

The reaction of the fetal heart to fetal activity is almost constant; in nearly every case the rate accelerates and frequently reaches a level of 160 or over. The reaction of the fetal heart to other stimuli is far less constant. Several illustrations have demonstrated fetal tachycardia from such causes as pressure of forceps, vaginal examination, uterine contractions and others, but it must be pointed out that very frequently these same causes produce a slow or irregular rate or no change at all; in fact, tachycardia is usually an exception rather than the rule.

A notion is prevalent among obstetricians, probably because of the reactions observed in the adult, that an oxygen deficiency of the fetus will produce tachycardia at first and subsequently bradycardia if the anoxia persists. This is not the usual reaction as was shown in previous studies[8] wherein the characteristic reaction of the fetal heart to oxygen deficiency was found to be a slow or irregular and slow rate. No relationship between fetal tachycardia and anoxia could be found in this study.

It is true that occasionally an initial acceleration of the fetal heart rate has been followed by a bradycardia in the presence of anoxia. A careful study of these observations reveals that the anoxia appeared *after* the tachycardia, thus establishing a relationship by chance rather than by cause and effect. Additional evidence against the belief that fetal anoxia produces a tachycardia was obtained when administration of oxygen to the mother failed to reduce the fetal tachycardia. The inability of oxygen therapy to reduce rapid fetal heart rates is in distinct

contrast with the results we have had by similar treatment of slow fetal heart rates. Anoxic fetal bradycardia can be controlled quickly and effectively by administration of oxygen to the mother as long as the oxygen transportation system remains intact.

There is one association of fetal tachycardia and anoxia which is occasionally observed, a tachycardia which sometimes follows the successful treatment of fetal anoxia. The course of events has usually been as follows: First there is a period of maternal anoxia which results in the characteristic slow or irregular and slow fetal heart. When oxygen is given to the mother, the fetal heart rate returns to normal. However, instead of remaining at normal, the rate continues to increase and is finally maintained for several minutes at a high level. Later the normal rate may be resumed (Fig. 7). For lack of a better term, this fetal tachycardia has been called compensatory, as it represents recovery from a period of bradycardia. From these observations it may be assumed that occasionally a rapid fetal heart rate may indicate recovery from anoxia when the tachycardia follows oxygen therapy, a complete reversal of the concept that tachycardia usually precedes bradycardia and is a sign of anoxia and impending distress.

Summary and Conclusions

1. From careful observations of the fetal heart rate throughout labor, rates in excess of 160 were found in 58 of 250 patients. In 44 of these labors the rate was transient; i.e., persisted for less than twenty minutes. In 14 instances the rate persisted for periods longer than twenty minutes. Only two infants had rates that exceeded 190 beats per minute and these for a very short time. Rates in excess of 160 during delivery were also uncommon: Seven infants only exhibited this finding.

2. There was no evidence that tachycardia indicated fetal distress. There were but three asphyxiated infants and one stillbirth in the group studied and none could be associated with the tachycardia.

3. Fetal movements were followed consistently by tachycardia though not always to a level of 160 beats per minute. Uterine contractions, application of forceps, pressure on the fetal head during rectal and vaginal examinations, and pressure of the fetal head against the perineum were sometimes followed by tachycardia although bradycardia was the reaction more frequently observed.

4. Anoxia was not found to be a cause of tachycardia in the fetus; this is in contrast to reactions usually observed in the adult.

From the results the author cannot subscribe to the notion that rapid fetal heart rates are either common or hazardous. Dangerous and unjustified obstetric intervention has been largely responsible for the unfortunate results commonly and erroneously attributed to fetal tachycardia.

References

1. Von Winckel, F.: Handbuch der Geburtshülfe, 1903.
2. Baumm, P.: Arch. f. Gynäk. **107**: 353, 1917.
3. Bartholomew, R. A.: Am. J. Obst. & Gynec. **10**: 89, 1925.
4. Freed, Frederick: Ibid. **14**: 659, 1927.
5. Richardson, Garwood C.: Ibid. **32**: 429, 1936.
6. King, E. L.: Ibid. **39**: 529, 1940.
7. Sontag, L. W., and Newberry, Helen: Ibid. **40**: 449, 1940.
8. Lund, Curtis J.: Ibid. **40**: 946, 1940.
9. Lund, Curtis J.: Ibid. **41**: 934, 1941.
10. Lund, Curtis J.: Unpublished data.
11. Windle, W. F.: Physiology of the Fetus, Philadelphia, 1940, W. B. Saunders Co.
12. Sontag, L. W., and Newberry, Helen: Am. J. Dis. Child. **62**: 941, 1941.

CONTINUOUS CAUDAL ANESTHESIA IN OBSTETRICS

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CAUDAL anesthesia in obstetrics was used apparently for the first time in the year 1919, but it did not make its appearance in America until 1923. Since then it enjoyed moderate popularity in this country. However, because of the element of risk, the procedure never became widespread, as safer anesthetics were available. Much of the early work was done in Baltimore and the method was used extensively in several of the larger hospitals. Baptisti[1] in 1939 reported 200 cases with excellent results. However, this method of obstetric anesthesia was discontinued throughout the city several years ago because of three maternal deaths in a total of approximately 600 cases. These deaths were all attributed to the anesthetic. Each of the deaths occurred in a different hospital after a large series of successful cases.

Very recently, Edwards and Hingson[2] published several papers on continuous caudal anesthesia which they used, not only for delivery, but as a means of producing a painless labor. They adapted Lemmon's[4] method of continuous spinal anesthesia to caudal anesthesia, and obtained striking success in 65 cases with no serious complications.

We were very much impressed by this report and a decision was made to try continuous caudal anesthesia in this institution despite the unfavorable experiences previously encountered.

We made several changes in the technique described by Edwards and Hingson as we believed that these innovations would increase the safety factor. A 1 per cent procaine solution was used instead of 1.5 per cent metycaine as shorter acting and less toxic. In addition, in order to eliminate the large injected doses of the syringe method which Edwards and Hingson employed, we devised a means of giving the procaine by a continuous gravity drip. This was done to simplify the

procedure and to decrease the attendant risks of large, rapidly injected doses of the anesthetic agent.

Technique

The procedure in detail which we employed was as follows:

1. It was necessary to give the patient a satisfactory enema to avoid fecal leakage when the rectal sphincter relaxed.

2. The patient should be made to void as she would find it impossible to do so once the caudal anesthesia has taken effect.

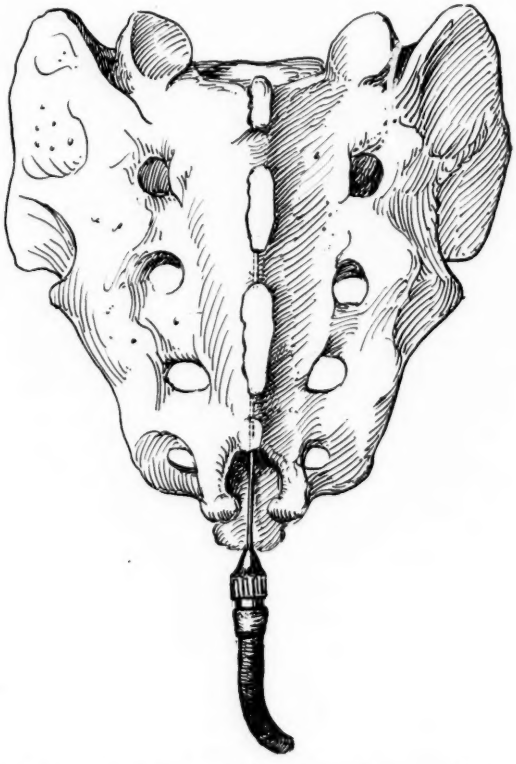

Fig. 1.—Showing insertion of needle in canal.

3. The patient was put in the knee-chest position, cleaned up with Scott's solution,* and draped.

4. The sacral hiatus was palpated, and 1 per cent procaine was injected to raise a skin wheal.

5. A 17 gauge continuous spinal needle was introduced through the wheal, and then guided into the sacral canal for a distance of about 2½ to 3 inches (Fig. 1).

6. The patient was turned on her side and a Luer-Lok syringe was then attached to the needle and an attempt was made to aspirate spinal fluid.

*Mercurochrome, 2%, in alcohol, acetone, and water (B. W. & Co.).

7. If no spinal fluid was obtained, a Pilling hard rubber tubing was then connected to the hub of the needle and the needle was securely taped down in the median raphe. The patient was then allowed to turn on her back.

8. The other end of the tubing was then connected by a glass adaptor to several feet of soft rubber tubing which led to a 250 c.c. graduated cylinder containing a 1 per cent procaine solution.

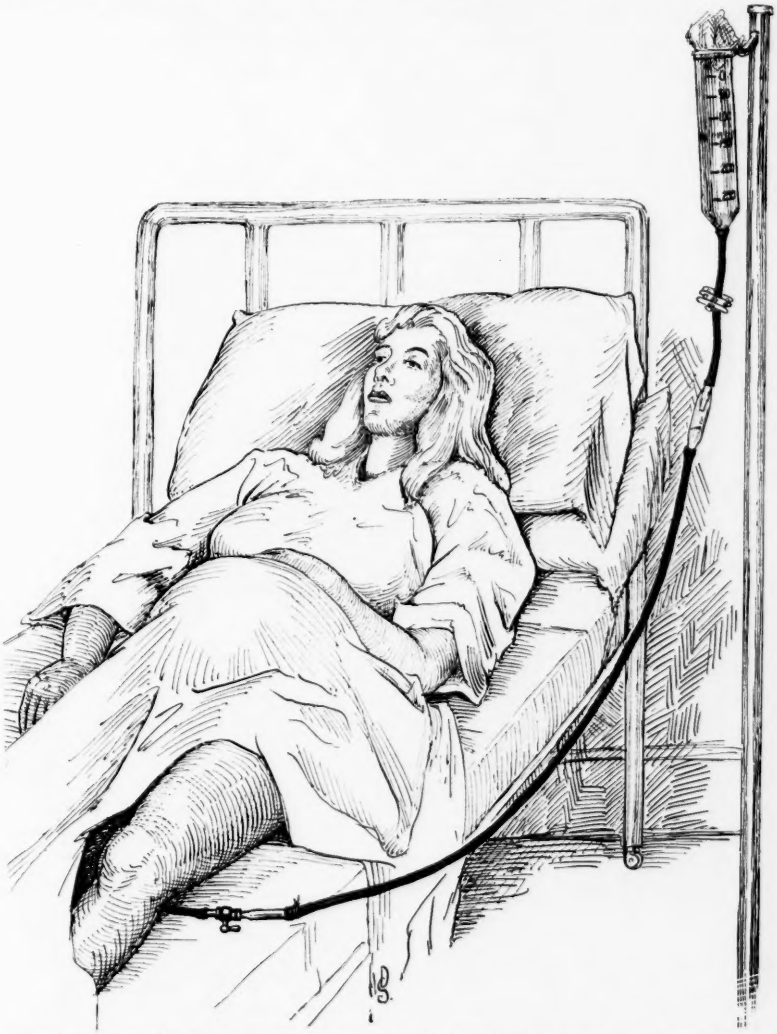

Fig. 2.—Showing position of patient, with graduate cylinder containing procaine solution, clamp, rubber tubing, and glass adapter.

9. The cylinder was suspended from a standard at a height of from 7 to 8 feet and the stopcock released. The procaine solution was then allowed to drip at a rate of 15 to 20 drops a minute.

Cessation of labor pains occurred in ten to fifteen minutes, and the solution was allowed to flow in continuously at this rate throughout labor and delivery.

With this method we hoped to avoid any accidents as any untoward symptoms would be detected before a large amount of procaine was introduced. It also eliminated the repeated periodic injections throughout labor and provided a means of administering a more even and regulated flow of the procaine.

Results

A total of 39 patients was given continuous caudal anesthesia, 31 primiparas and 8 multiparas. The anesthesia was started as soon as possible after admission to the hospital if regular uterine contractions could be felt. The amount of dilatation was unimportant and several patients were given the anesthesia with good results although the cervix was dilated 2 cm. or less.

In this series we had 39 living mothers and 38 living babies. The lone fetal death was a macerated fetus and no fetal heart was heard on admission to the hospital. For purposes of clarity, the first 38 cases of the series will be presented as an entity and the last will be presented in detail.

In all cases complete relief from pain was noted in from ten to fifteen minutes. Uterine contractions continued unabated, yet the patient was unaware of it. The majority of the patients would lie comfortably in bed throughout labor, either reading a magazine or conversing with their neighbors. The nursing problem, which is so important these days, was considerably lessened, as these patients required little attention. The contrast in two adjoining beds, one patient resting quietly under caudal and the other noisy and attempting to get out of bed under nembutal or paraldehyde analgesia, was most striking.

Labor was shortened with caudal anesthesia. The average length of time for the first and second stages of labor together for our eight multiparas totaled two and one-half hours. This figure was attained despite several abnormal presentations and despite extremely early administration in some cases. For the 30 primiparas, the average length of time was four hours, although one-half of the patients delivered in three hours or less from the time of administration. Several cases were successfully kept under caudal for ten hours or more, the longest being twenty hours, in which time the patient received 900 c.c. of procaine with no untoward effects. The shorter duration of labor is undoubtedly due to relaxation of the cervix and perineum.

We have found caudal anesthesia to be of particular value in dystocia cases. It practically eliminated cervical dystocia and it reduced dystocia to actual cephalopelvic disproportion. Cases of this sort could be given a thorough test of labor without fear because the patient did not become exhausted and she was able to cooperate fully with the wishes of the nurse and doctor. It was a simple matter to keep her well hydrated and fed if it was so desired.

Ten patients were delivered spontaneously and 28 required operative interference. Most of the low forceps were done electively although four were indicated. Though the caput descended to the perineal floor, the loss of the sensation of rectal pressure prevented these women from bearing down unless encouraged. This practically eliminated the possibility of precipitate deliveries in bed. When full dilatation was reached, the obstetrician had full cooperation of the patient, and she could be en-

couraged easily to bear down. In this manner we were able to deliver 10 patients spontaneously. Three cases were breech deliveries and no difficulties were encountered.

In 35 cases no supplementary anesthesia was needed. No pain was felt despite forceps or episiotomy repairs. In three cases, a Kielland forceps for transverse arrest, an internal podalic version for a compound presentation, and a high midforceps for a persistent occiput posterior with cephalopelvic disproportion, inhalation anesthesia was utilized for delivery. The elimination of an inhalation anesthetic seemed especially valuable for the three cardiac, one nephritic, one tuberculous, four toxemic, and one upper respiratory complications which were present in this group of patients at the time of delivery.

The absence of analgesic effects upon the fetus was most striking at delivery. Except for one macerated fetus, every baby cried in less than one minute and the vast majority cried before the delivery was completed.

The difference in the amount of bleeding at delivery was also noticeable. Although no attempt was made to measure the amount of blood loss accurately, the estimated amount was far less than with inhalation anesthesia. There were no cases of post-partum hemorrhage.

Four patients with pre-eclamptic toxemias were given caudal anesthesia. In all cases some drop in blood pressure was noted. No other medication was given. Although this is inconclusive, further studies in this direction would not be amiss.

Complications

The complications that were noted in the order of their frequency were nausea and vomiting, dizziness, drowsiness, and in one instance, diplopia. These were probably mild systemic reactions to the procaine. A frequent complaint was low back pain during the first twenty-four hours postpartum which was often so severe as to require one or two doses of morphine before relief could be obtained. Two patients may have developed a neuritis, as they constantly complained of back pain during their entire hospital stay, and complete relief was not obtained until two weeks following delivery. When the series was first started 18 and 19 gauge needles were used. However, 5 of these needles broke while in use. Three were merely pulled out by the protruding fragment, but in two cases a small skin incision was made before the needle could be extracted. No needles broke after the 17 gauge needles were put in use. Despite these complications the method seemed most satisfactory, as the advantages seemed to outweigh by far the disadvantages.

Our thirty-ninth case was a 22-year-old primipara at term in early labor. She had a 3 cm. dilatation, with the cervix 50 per cent effaced and the vertex at the level of the spines. Pains were fairly strong and they recurred every three to four minutes. The fetal heart was heard in the right lower quadrant and was of good quality. The fetus was palpated in the R.O.A. position. The patient was given an enema and told to void. She was put in the knee-chest position and a 17 gauge needle was introduced into the caudal canal. Suction was made with a syringe and no spinal fluid was obtained. Unfortunately, since the patient was complaining of her pains quite frequently, we did not adhere strictly to our accepted method, and she received 10 c.c. of 1 per cent

procaine by an injection with a syringe. We then hooked up our apparatus and allowed the procaine to drip in by gravity.

After five minutes the patient began to complain of some tingling in her feet, a common symptom with caudal anesthesia, but she was able to move her toes. Shortly thereafter, she suddenly lost the power of speech, became very cyanotic, and went into collapse. The patient had respiratory paralysis and her blood pressure and radial pulse disappeared. She was given artificial respiration until she could be intubated and then her respirations were maintained with oxygen through the intratracheal tube. Caffeine, coramine, and adrenalin were administered, as well as heat and intravenous fluids. Respirations were not re-established for forty-five minutes, and she had spinal anesthesia for six hours. The caudal had been discontinued at the first signs of distress, but this was not before the patient had received a total of 30 c.c. of procaine solution. The patient returned to consciousness one and one-half hours later, and ten hours later she delivered a living child. The mother and baby made an uneventful recovery, and were discharged on the tenth day in good condition.

Conclusions

Although there were no fatalities in this series, we feel that no matter how the procaine is administered, the danger of an anesthetic death is still very real. Despite its many advantages, we do not feel that continuous caudal anesthesia is a procedure to be used indiscriminately. The inherent risk of introducing the needle unknowingly into the spinal canal is constantly present. It may have a place in cases where other forms of analgesia or anesthesia are contraindicated, but we do not believe it is as safe as the anesthetics now commonly employed. We believe that its use should not become routine, particularly in smaller hospitals where a competent anesthetist is not always available to cope with the serious complications resulting from an accidental introduction of the anesthetic agent into the spinal canal.

References

1. Baptisti, A.: Am. J. Obst. & Gynec. **38**: 462, 1939.
2. Edwards, W. B., and Hingson, R. A.: Am. J. Surg. **67**: 459, 1942.
3. Lahman, A. H., and Mietus, A. C.: Surg., Gynec. & Obst. **74**: 63, 1942.
4. Lemmon, W. T., and Paschal, G. W., Jr.: Pennsylvania M. J. **44**: 975, 1941.

Ohkusa, M.: The Role of Vitamin A, Vitamin D and Cervical Erosion, Jap. J. Obst. & Gynec. **23**: 39, 1941.

It is well known that vitamin A has a favorable effect by epithelization and that vitamin D is effective in certain cases of eczema. Based upon these facts Ohkusa applied vitamins A and D to cervical erosions. He combined this treatment with hot lysol douches. He maintains that vitamins A and D are effective in curing cervical erosions. This is particularly true of erosions found in acute gonorrheal infections. Cod-liver oil contains relatively small amounts of vitamins A and D, hence it is best to use a special ointment containing large amounts of these vitamins.

J. P. Greenhill.

GROUP INCIDENCE OF HYPERTENSIVE-ALBUMINURIC PREGNANCY UNDER THE NEW CLASSIFICATION*

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IN 1936 before this Association we presented a paper entitled "Recent Experience With a New Classification of Pregnancy Complicated by Hypertension and Albuminuria."[1] The material covered the accumulation of eighteen months and hence was of value only in illustrating the groups in the classification. The purpose of the paper was to present the classification and justify its creation, and to attempt definite definitions of each group. In 1930,[2] before this Association, in a communication embodying an effort to correlate 1,100 cases classified crudely from the Boston Lying-in Hospital Toxemia Clinic with the Williams-Stander classification, I stated that "a cooperative study throughout the United States under *a single classification* is highly desirable."

Subsequent to the 1936 meeting of this Association, due to the immediate interest of Drs. Cosgrove and Adair, The American Committee on Maternal Welfare "appointed a committee to develop an acceptible classification of the toxemias of pregnancy based on available scientific and clinical knowledge of these diseases." Robert D. Mussey, Chairman of this committee, published in April, 1940, the results[3] of the work of this committee.

With the publication of this report this committee ceased to function as such.

In 1939 before the First American Congress on Obstetrics and Gynecology we offered a further contribution entitled "The Classification of Hypertension and Albuminuria in Pregnancy"[4] in which, after four years' experience, we presented a modified classification.

The purposes of the present paper are three: (1) To crystallize the product of seven years' effort for an acceptable tentative classification and to analyze future possibilities. (2) To report gross figures in the groups from the clinic of the Boston Lying-in Hospital in the five years 1935 to 1939 inclusive. (3) To consider practical limitations of these classifications, as used, especially as to subgroups.

1. We can restate the purpose of a generally used tentative classification as follows: To accumulate as rapidly as possible data on different

*Presented at the Fifty-Fifth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 10 to 12, 1942.

groups of hypertensive albuminuric pregnancies (more rapidly than this can be done by any one man or clinic) and from analysis of these data in quantity to draw factual conclusions on matters pertaining to these serious complications of pregnancy now too frequently impressionistically considered because of individual limited experience with group classification. This especially in the matter of clinical prognosis; but as well such a division can serve as a sound basis for all other approach. At the Washington Conference, for example, etiologic, physiologic, metabolic, endocrinologic, and clinical discussion was so based not only by plan, but in much that was extemporaneous, instinctively. In short there is a general feeling for this sort of division among interested men at this stage in our ignorance of this subject.

Since this stated purpose is defeated *ipso facto,* unless a majority of clinic directors are in some accord, we must consider frankly the reaction in the last six years to this effort. It is clear that in order to accumulate and analyze the data and pursue allied investigation of set problems, a high degree of cooperative effort must exist between individual clinics and some properly equipped and manned bureau for collection. It is equally clear in retrospect that the American Committee on Maternal Welfare's appointed "Committee on Classification" was not equipped and manned to be the receiving body for this material and investigation. At the Washington Conference of the United States Department of Labor, Maternal and Child Health Division, Children's Bureau was stated to be so equipped and Dr. Edward Daly, Director, said the bureau was willing to act as a collection agency for these data.

We may consider briefly reaction to the attempt to acquire an acceptable tentative classification chronologically. The original paper before this Association was well received as evidenced by the appointment of a Committee on Classification. The work of this committee met with general approval as evidenced by the "acceptance in principle" of the classification in many clinics in the country. However, we left the meeting at the First American Congress with the feeling that, in general, the criticism in the discussion was not constructive and that each discussant preferred his own classification. The Washington Conference reaction was, on the whole, favorable to the work of the Committee on Classification; but failed in our opinion to take cognizance of two important points which will be discussed later. Dieckmann's *Monograph* opens with acceptance of the Committee's classification and includes a table showing the incidence of the different groups in a small number of cases from three clinics. Dexter and Weiss[7] in their book shy away from these attempts at classification and approach the subject on the basis of different courses of hypertension in pregnancy. Tillman[8] emphasizes the difficulties of fitting all cases to a classification but agrees with the idea that such an attempt is useful.

2. We now report in summary the gross figures from the Boston Lying-in Clinic during the five years 1935 to 1939, inclusive. This material includes that in our original paper.[1]

A total figure of 1,541 cases was studied, divided as follows:

Group A, i.e., Disease independent of pregnancy,	169 cases, 11%
Group B, i.e., Disease dependent on pregnancy,	1,370 cases, 89%
Total	1,541 cases, 100%

These percentages are exactly the same as in the preliminary study of eighteen months.

For better perspective, however, it should be stated that of Group B, 1,186 cases, or 86.5 per cent, were "mild pre-eclampsia," and since this group represents a little of everything and is frequently not definable at any given time, if ever, its inclusion distorts the true picture of the relative incidence of Groups A and B from a practical clinical standpoint since rarely is it of much importance in this respect.

Group B shows:

"Pre-eclampsia," mild	1,186 cases, 86.5%
"Pre-eclampsia," severe	164 cases, 12.0%
Eclampsia	30 cases, 2.2%
Total severe pre-eclampsia and eclampsia	194 cases, 14.2% of Group B

A breakdown of figures in Group A (i.e., disease independent of pregnancy) shows (and part of this is estimated due to the fact that in some years the reports did not distinguish between "chronic nephritis" and "essential hypertension"):

	1936 1938 1939
Essential hypertension	76 cases
Chronic glomerular nephritis	14 cases
Total	90 cases in which a differential diagnosis was made.

"Essential hypertension including chronic nephritis" without differential diagnosis.

1935	28 cases
1937	41 cases
	69
	90
	159
Pyelonephritis in all years	10
Total "Group A"	

In summary, in percentages, our five-year figures show for Group A estimated in part:

Essential hypertension	75, 80% (probably too low)
Chronic glomerular nephritis	20, 25% (probably too high)
Chronic pyelonephritis	0.6% (probably too low)

If we omit mild pre-eclampsia (largely unknowns), we have

Group A	169 cases	44%
Group B	194 cases	56%
	363 definitely diagnosed cases.	

We have no definite statement of cross-indexing in the two groups. In this whole group the gross fetal death rate was 105 per thousand live births as against a general rate in the hospital in 1941 of 66 per thousand.

For purposes of illustration and in contrast to the above gross figures the only fairly complete report in the five-year period is given below:

Toxemia Clinic. Report of Boston Lying-in Hospital, 1939

1. The total number of patients who attended the toxemia clinic was about 10 per cent of the total patients from all the pregnancy clinics. Those who had definite toxemia of pregnancy, including cases of chronic vascular or renal disease complicating pregnancy, was 7 per cent.

The following statistics are presented:

New patients:			
Hospital	287		
Out-patient	57		
		344	
Visits:			
Subsequent visits		706	
Follow-up visits		63	
Total visits			1,113
Deliveries:			
Primiparous		101	
Multiparous		136	
			236
Toxemias classified:			
Pre-eclampsia, Grade 1 (mild)		174	
Pre-eclampsia, Grade 2 (severe)		26	
Eclampsia		4	
Hypertension		23	
Nephritis		2	
Pyelonephritis		5	
Cortical necrosis of the kidney		2	
			236

All the maternal deaths were in women over the age of thirty-five. Three of these women gave evidence, obtained at autopsy, of previous hypertensive vascular disease. It again emphasizes that caution must be exercised in this age group with vascular hypertension.

2. *Eclampsia.*—There were four cases of eclampsia with one death. Two cases were emergencies, one of which died. Three had ante-partum, and one post-partum convulsions. Two were known to have had normal blood pressures and kidney function prior to the onset of the disease and both recovered. The status of the vascular and renal systems of one patient was unknown prior to the onset of the disease, while in the patient who died autopsy revealed previous arteriolar changes.

3. *Fetal Deaths.*—

	GRADE 1 MILD	GRADE 2 SEVERE	HYPERTENSIVE DISEASE	TOTALS
Delivered patients	174	26	23	223
Stillbirths	4	4	6	14
Neonatal deaths	4	1	0	5
Total per cent	4.65	19.2	26.1	8.97
Corrected per cent:				
Stillbirths	1.72	11.5	4.35	
	1.72	.0	.00	
	3.44	11.5	4.35	

In addition to the above there were two mothers with chronic glomerulonephritis, both of whom delivered nonviable stillbirths. Out of five cases of chronic pyelonephritis, only one baby was discharged from the hospital alive.

The fetal mortality in the toxemic group has been materially decreasing over the past five years. We believe this can be explained by two factors: first by the more frequent inductions of labor near the thirty-fifth week of pregnancy, and second, the presence of an excellent premature nursery to allow the pediatric and nursing staffs to salvage each year an increasing number of premature babies. To further emphasize this, there were only five stillborn infants in all the groups whom the obstetricians might have saved if induction of labor had been performed at an earlier date.

Comment

We have in the "classification idea" along these lines something acceptable to most obstetric clinics for present use. Its seed has now been planted for seven years; it budded with the publication in 1940 of the report of the Committee on Classification;[3] it flowered mildly at the Washington Conference in 1941.[5] As it stands now it appears to us to need still further pruning to bear its hoped for fruit.

One-half its purpose has been fulfilled; we have a common clinic language in the subject. The other half, the accumulation of data for general information, is unfulfilled.

The Committee on Classification failed to realize that for data collection purposes it is important to distinguish between mild and severe chronic glomerular nephritis and perhaps mild and severe pyelonephritis, since quite different prognoses and results exist in these subgroups, certainly in the former. (These are definitely defined in our papers of 1936[1] and 1939.[4])

The Washington Conference, pushed for time because of the very considerable amount of ground it was attempting to cover (and an unbalanced amount of this was given to Classification discussion) planned no definite mechanism for collection of data, hastily voted to accept the Committee's Classification without consideration of the subgroups

aforementioned and set the time for group indexing as of the departure of the patient from the Hospital. This time may be all right for the individual clinic although we do not believe this, but is certainly not so for group data collection, because it contradicts the principle we learned from Herrick and Tillman, namely, that some follow-up at least, and the longer the better within practical limits, is vital in grouping these patients. The Conference also dwelt at length on the loss of patients when a policy of follow-up is pursued but, as Herrick said in Washington, "It does not matter whether you get all back or not, you still have enough for a good cross section. In both private and hospital practice an adequate percentage for satisfactory study will report."

Conclusions

We therefore make the following specific recommendations.

1. That definitely defined subgroups in *Group A* be incorporated in the classification.

2. That a copy of the Proceedings of the Washington Conference on Eclampsia 1941 be made available to each clinic using the classification.

3. That arrangements be made between interested clinics and the Chairman of the so-called permanent Committee to supply the Washington Bureau with a limited round number of carefully studied cases each year on a set date, the number to depend on the size of the clinic and its personnel ability to study the cases; cases of the previous year, i.e., at the end of twelve months after hospital discharge.

4. That these reports take a set form somewhat as in our hospital report of 1939 (shown above) with somewhat similar comments but that, in addition, fetal and maternal morbidities (including specific statements on degree of prematurity in terms of weeks gestational age checked against weight); and pathologic report on all available material *including placentas,* be incorporated *in each group;* and a definite statement of cross-indexing, as this report does not do.

5. Thus and only thus, in our opinion, can we obtain satisfactory information with not too great individual effort and with the understanding that some clinics are better equipped and manned than others to supply data in quantity.

References

1. Kellogg, F. S., Smith, J. A., Teel, H. M., and Reid, D. E.: Am. J. Obst. & Gynec. **33**: 300, 1937.
2. Kellogg, F. S.: Am J. Obst. & Gynec. **21**: 275, 1931.
3. Mussey, R. D., et al.: The Mother, Chicago, 1940, Am. Com. Mat. Welfare.
4. Kellogg, F. S., and Reid, D. E.: Proc. 1st Am. Congress on Obst. & Gynec., p. 165, 1941.
5. Conference on Eclampsia, Children's Bureau, Dept. of Labor, Washington, D. C., January, 1941.
6. Dieckmann, W. J.: Toxemias of Pregnancy, St. Louis, 1941, The C. V. Mosby Co.
7. Dexter, Lewis, and Weiss, Soma: Pre-Eclamptic and Eclamptic Toxemia of Pregnancy, Boston, 1941, Little, Brown & Co.
8. Tillman, A. J. B.: J. A. M. A. **120**: 587, 1942.

Discussion

DR. NICHOLSON J. EASTMAN, BALTIMORE, MD.—The classification of the toxemias of pregnancy is of the utmost practical importance. Patients who have had hypertension during a previous pregnancy are continually asking about the chances of going through another pregnancy satisfactorily. It is only by observing and cataloguing a large number of cases, all carefully studied and followed, that we can establish the prognosis of these patients. Dr. Kellogg's recommendation that carefully studied cases be submitted each year for analysis and review is an excellent one. It will be only a modicum of cases, however, that lend themselves to critical study, because of lack of information. Our own greatest difficulty in classifying cases of toxemia is that a history throughout pregnancy is necessary. The main dividing line used by the Committee in differentiating chronic from acute toxemia is the time factor. Do the signs develop before or after the twenty-fourth week? Very often patients develop toxemia later; and not knowing what has transpired early in pregnancy, it is impossible to classify such cases, at least on the criteria used by this classification.

In our experience, chronic hypertensive vascular disease is becoming an increasingly frequent cause of maternal death. Fifteen years ago 60 to 70 per cent of our deaths from toxemia of pregnancy were the result of eclampsia. Little by little, as a result of better prenatal care, and a better understanding of eclampsia, deaths from eclampsia have decreased to such an extent that they make up only 6 to 8 per cent of the toxemic deaths. Conversely, whereas fifteen years ago, 20 per cent of our toxemic deaths were due to chronic hypertensive vascular disease; today 70 per cent are the result of that condition. We believe, accordingly, that this group of chronic hypertensives deserves increasing attention.

DR. SAMUEL A. COSGROVE, JERSEY CITY, N. J.—Discussion of what constitutes the several groups in a classification brought before us this morning by Dr. Kellogg is not pertinent. His plea, first of all, is for a common medium of expression. Each one of us may have our own ideas as to modifications of that medium of expression, but unless we all use the same medium we cannot get together the great mass of material which is so important. We must agree, for the present at least, on the basis which Dr. Kellogg and the Committee on Maternal Welfare have suggested. By and large it is not a bad system. I think it necessary to point out that a mere pooling of large numbers of cases will not accomplish the desired result. If the agency which will handle this immense national material is merely an uncritical indexing agency, that effort will necessarily go to waste. There must be a sorting of the material that comes in by a competent critical agency before it is turned over to the indexing agency.

Components of this pool from various sources will be based on studies of varying competency, and differing durations of observation after the occurrence of the toxemia. Therefore, as these studies come in from individual clinics, they should be evaluated before being drawn into a pool from which broad deductions are to be attempted.

DR. GEORGE W. KOSMAK, NEW YORK, N. Y.—I believe that the most noteworthy point brought out in Dr. Kellogg's paper is the need of some central body to do what Dr. Cosgrove has suggested, and I think the most available source for the development of such a body is one of the national societies interested in this particular field. Without intending this to be derogatory, I doubt whether a Government agency which is interested in the statistical side of this question would be the one to undertake this study. An organization such as this Association could well take upon itself the duty of doing exactly what has been suggested. We have had a number of people who have tried to do this, but we are not getting anywhere

with it. A resolution brought up for consideration by this Association, and providing the necessary means, would be a most worthy object of attack for this particular problem.

DR. A. N. CREADICK, NEW HAVEN, CONN.—There are two particular points which should be emphasized. Most clinics have associated with the obstetrician an internist and a chemist. These associates have become interested in the problem of toxemias, have criticized our clinical classification, and substituted a chemical nomenclature. However, I still think we should have associated with us medical men of the best caliber obtainable.

The second point is the use of nomenclature from a clinical point of view. At last we have begun to talk about the same things, and we had better persist in following Dr. Kellogg's nomenclature. A biochemist should be associated with this Committee, but we should continue to use the clinical nomenclature so that we will know what we are talking about.

DR. GEORGE F. PENDLETON, KANSAS CITY, MO.—I am not satisfied with this classification. If you are going to set up a classification, it should be consistent, either clinical or anatomical. In the present terminology, for instance, we use the term eclampsia, which is a clinical entity, and then we mix this with pathologic terms as nephritis or pyelonephritis.

DR. A. J. RONGY, NEW YORK, N. Y.—Eclampsia is not a hereditary disease, but there is definitely a constitutional type, which is more prone to develop eclampsia. The experienced obstetrician in many instances should be able to anticipate the type of pregnant woman who is likely to develop toxemia in pregnancy. It is a well-known clinical fact that a woman, long-necked and long-boned, with a slightly enlarged thyroid, seldom develops eclampsia. I believe that our present knowledge of etiology of eclampsia is not sufficient to warrant any classification of the disease.

I believe that it is more important to watch these patients from a clinical standpoint and rely more on clinical symptoms than to be guided by the laboratory findings. Those patients who develop severe toxemia usually have a premonitory period and begin to complain of general malaise, loss of appetite, headaches, epigastric pain, visual disturbances, and occasionally itching of the skin, accompanied by an increase in the blood pressure and albumin in the urine. When the clinical symptoms do not improve or subside under treatment, the pregnancy will have to be interrupted.

DR. KELLOGG (closing).—I did not intend to bring up the question of what constitutes eclampsia, or suggest perfection for this classification. We would welcome a better classification from those who criticize that which we propose.

There are many subgroups, small in any one clinic or individual's experience. There is no question, for example, that there is chronic glomerular nephritis in pregnancy. There may be cases which are followed by such complete recovery that if the patient is studied with the utmost care six or eight months afterward you could not determine that she had had it. We do not yet know the prognosis for these patients in their future life as a whole or in future pregnancies. The only way to discover this is to get material for these minor groups, from a great many sources.

It is problematical as to who will carry on the work. Nevertheless, we wish to go on record at this time with this plan as desirable work for some future date.

THE RESPONSE OF THE HUMAN UTERUS TO EPINEPHRINE*

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LABORATORY observations have frequently been transferred directly to clinical practice without the necessary critical study to determine their value or safety. Such superficial observations are frequent in medical literature and, once a positive statement has been made, it is copied repeatedly without recheck so that it is not long before this poorly established concept becomes a quoted dictum of therapy. Once these concepts have been made a printed record, they assume authority all out of proportion to their value, and the reader fails to critically analyze the evidence which led to that conclusion. It then requires a large accumulation of negative information to compensate for this one positive statement. This seems to be true of the recommended use of epinephrine in treatment of tetanic cervix and hourglass contractions of the uterus.

Because of confusion involved in terminology, throughout this report we shall use the term "contraction rings" to include all of those variants of uterine contraction known as Bandl's ring, retraction rings, hourglass contractions, and others. While it is possible that these may represent different clinical entities, we are inclined to agree with Rudolph,[1] who describes these as an exaggeration of the normal process of uterine contraction and retraction, and that these pathologic states represent an accentuation to an abnormal degree of physiologic processes.

A contraction ring may be defined as a localized area of tetanic uterine contraction which interferes with the process of labor (Fig. 1). The best evidence seems to suggest that this is a disturbance in uterine activity resulting from abnormalities within the uterus itself. Whether there is a disturbance in the neurogenic reflex arcs of the sympathetic system is still unknown. While many factors (pituitrin, intrauterine manipulation, forceps, etc.) may precipitate this process, contraction rings develop most frequently as a complication of fatigue, dehydration, and prolonged labor.

One of the earliest reported studies of the action of epinephrine on the uterus was made in 1912 by Dale and Laidlaw,[2] using the isolated intact uterus, and uterine strips of the cat and guinea pig. These observers noted that the spontaneous contractions of the uterus were abolished by the addition of epinephrine. In 1913 Gunn[3] studied the isolated human uterus (both intact and muscle strips) and reported that epineph-

*Read at a meeting of the American Federation for Clinical Research, Minneapolis, 1942.

rine stimulated the uterus under these conditions. In 1927 Rucker,[4] working on the hypothesis of the relation of the sympathetic system to uterine contractions, reported a relaxation effect of epinephrine on the contraction rings in dystocia. His records are in part graphic, but for the most part are clinical interpretations. Since that time a considerable number of observations have been made by many authors with conflicting opinions, some feeling that epinephrine is motor to the human uterus[5, 8, 10, 14] and others that it is inhibitory.[6, 7, 9, 13, 15-17]

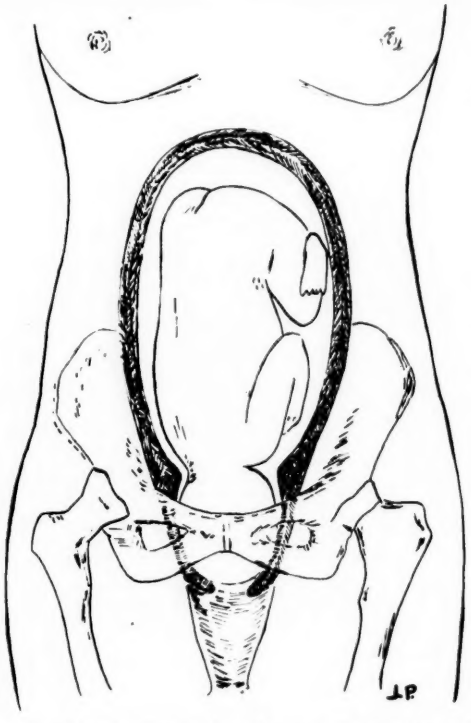

Fig. 1.—Diagrammatic drawing of contraction ring.

Clinically, epinephrine *alone* has seldom seemed satisfactory for the relaxation of these contraction rings. Because of the unsatisfactory clinical results from the use of epinephrine, and the great differences of opinion regarding its effect, it seemed wise to restudy this subject and try to obtain information on the human uterus.

Methods

During the course of our studies on uterine motility, we attempted to assay the effect of the administration of epinephrine on the laboring and post-partum uterus. While epinephrine was given both intravenously and intramuscularly, it was usually given intravenously in order that we might more easily record the beginning and end of the response obtained. Epinephrine solution 1:1000 was given in saline in

one to two minim amounts; while this is quite small it approximates that used in clinical practice.

The observations on the post-partum uterus were made on patients who were entirely normal and were between the fourth and eighth post-partum day. Under sterile conditions a Hegner bag was inserted in the uterus and connected by water to a mercury manometer and kymograph so that graphic records were obtained (Fig. 2).

The observations on the laboring uterus were made by similar direct manometric methods. On several occasions we were privileged to connect a Voorhees' bag, being used for the control of hemorrhage in placenta previa to a recording kymograph.

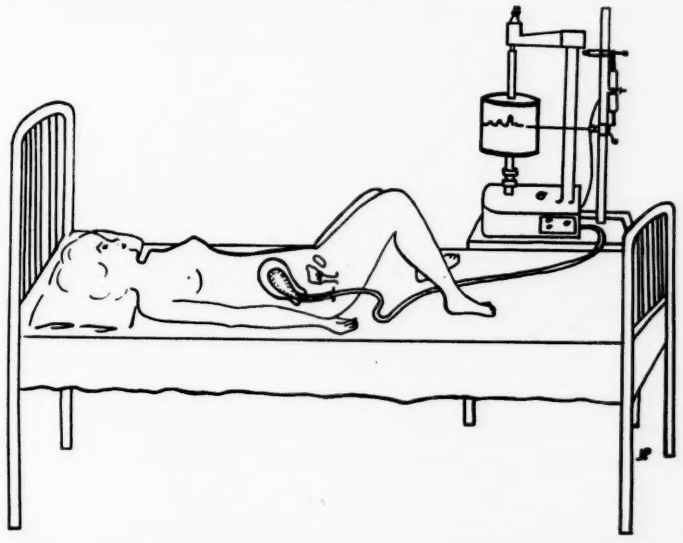

Fig. 2.—Method of obtaining curves. Hydrostatic bag was inserted into the uterus with antiseptic precautions. Contractions were recorded by a water-mercury float manometer.

Following the introduction of the bag a period of adjustment was permitted which varied from thirty to ninety minutes. The effect of epinephrine was studied on two types of uteri, laboring and puerperal. Some of the puerperal uteri exhibited spontaneous rhythmic contractions and in others the contractions were induced by an oxytocic (pituitrin or ergot).

Results

The human uterus responds to intravenously injected epinephrine quite consistently by contraction, typical examples of which are to be found in Figs. 3 through 8. These induced contractions varied in magnitude but in general they represented an extrasystole type of response. This appears as an induced contraction which occurs prematurely in the cycle and is followed by a compensatory pause. If the uterus was contracting at the time of injection a greatly heightened contraction occurred (Figs. 4, 6, 8). No difference in response was observed between the spontaneously contracting uterus and the uterus with an oxytocically induced rhythm (Figs. 6 and 7). In no circumstances was there a drop in tone indicating a relaxation.

The duration of the effect of epinephrine on the human uterus varied somewhat but in general lasted less than four minutes or until the next independent contraction. This effect is manifested by a zone of inactivity which compares in type to the pause which follows extrasystole in the cardiac. There was no drop in the uterine base line, so

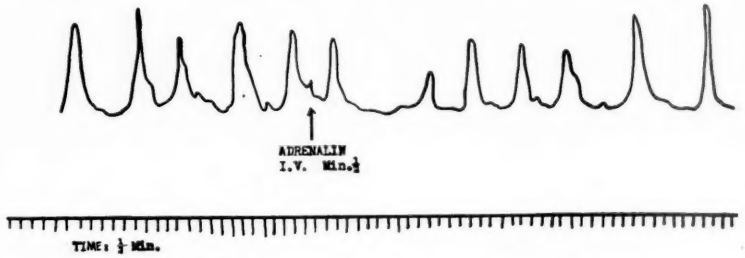

Fig. 3.—Laboring uterus; epinephrine injected intravenously.

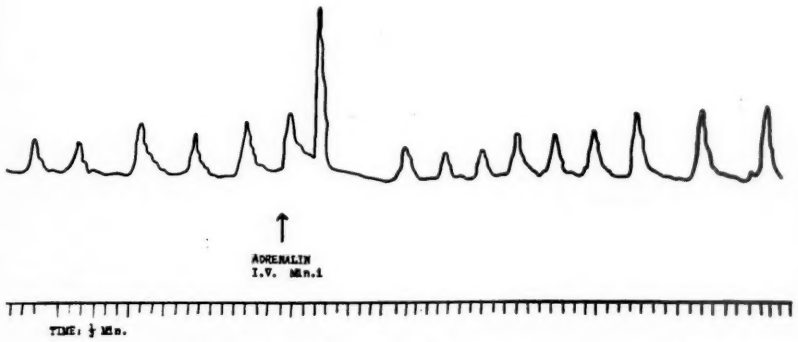

Fig. 4.—Laboring uterus; epinephrine injected intravenously.

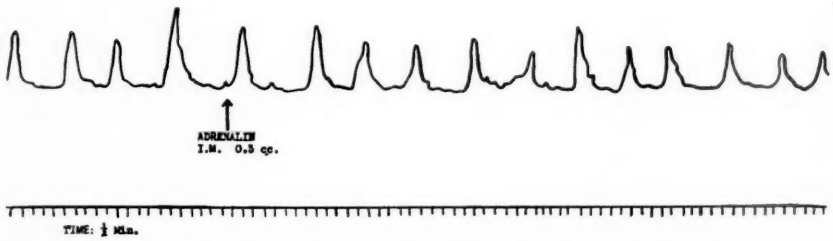

Fig. 5.—Laboring uterus; epinephrine injected intramuscularly.

that we believe this represents a disturbance in rhythm rather than an alteration in uterine tone. We are unable to demonstrate the increased tone recorded by Woodbury[5] or Gunn.[3] Throughout these observations no evidence was adduced to support the theory that the cervix relaxes under the influence of epinephrine. Had the cervix relaxed the hydrostatic bag would have been expelled by the uterine contractions and this was not observed. The serial-recording observations of Ivy (Fig. 7) indicate that at least for the monkey, the cervix and body of the uterus react in the same manner, i.e., by contraction.

These findings are in accord with the observations of Woodbury and others;[5] Ivy and others;[6] and Bourne and Burn as far as rhythm changes are concerned. Ivy,[6] and Bourne[7] have recorded the same type of curves obtained in our studies. Thus the confusion that has existed

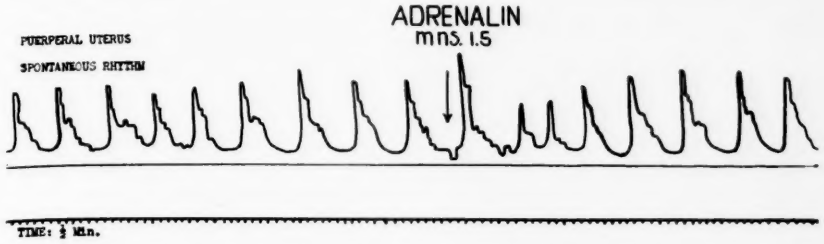

Fig. 6.—Puerperal uterus, spontaneous rhythm; epinephrine injected intravenously.

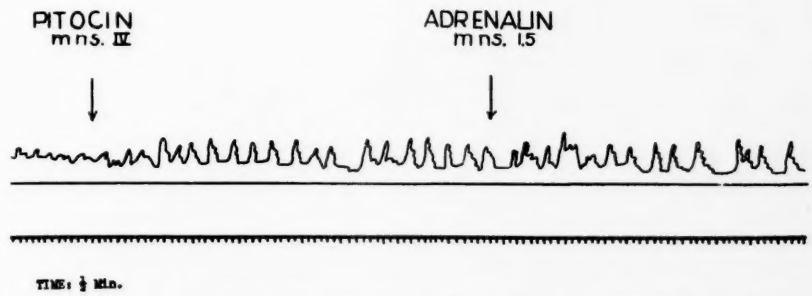

Fig. 7.—Puerperal uterus, pitocin induced rhythm; epinephrine injected intravenously.

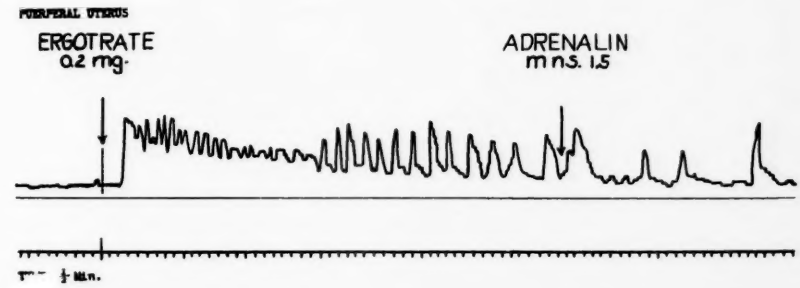

Fig. 8.—Puerperal uterus, ergotrate induced rhythm; epinephrine injected intravenously.

regarding the response of the human uterus to epinephrine resolves itself into an interpretation of what constitutes inhibition. The apparent inhibition claimed by one group, we believe, is the refractory state of muscular activity rather than a drug effect.

From our own observations and a more critical interpretation of the curves published in the literature we believe that epinephrine stimulates the human laboring and puerperal uterus to contraction. Table I, modified from Reynolds,[11] explains some of the differences of opinion in the literature. Animals vary in their response to epinephrine, and in cer-

tain species (Table I, Group II) vary with the status of the uterus. We recognize that the normal laboring uterus and the puerperal uterus may not respond in the same manner as an abnormally contracting uterus showing contraction ring.

TABLE I. UTERINE RESPONSE TO EPINEPHRINE OF VARIOUS LABORATORY ANIMALS

(REVISED FROM REYNOLDS[11])

	ANIMAL	GRAVID	NONGRAVID
I.	Guinea pig, Rat, Mouse	Inhibitor	Inhibitor
II.	Cat, Dog	Motor	Inhibitor
III.	Rabbit, Squirrel, Ferret, Hedgehog, Monkey	Motor	Motor
	Human	Motor	Motor

That epinephrine alone seldom adequately relaxes these contraction rings, has been the clinical experience of many obstetricians. Most authors[13, 15-19] recommend the combined use of epinephrine and a general anesthetic. If one recalls that intramuscularly injected epinephrine does not become effective for several minutes, it is more likely that the relaxation produced under this schedule is the result of the anesthetic. It is our own impression from clinical observations that no advantage is obtained from the use of epinephrine in contraction rings. This opinion is based on both abdominal palpation and vaginal examination of the patients treated with epinephrine.

If epinephrine were simply valueless in the management of contraction rings, our observations would be of academic interest only. However, in a fatigued, dehydrated and shocked patient who is in the excitement phase of ether anesthesia, epinephrine carries a serious potential risk which we are not warranted in inflicting on our patient unless we can demonstrate clear-cut and unquestioned value. Under such conditions epinephrine may very well further contribute to the development of shock by increasing the spasm of already constricted arterioles, and thus continue the vicious cycle of capillary stasis, tissue anoxia, and eventual circulatory collapse.[20] Epinephrine also increases the irritability of an already rapid heart,[21] further accelerating it to the point of diminishing volume output, and may initiate a disturbance of rhythm such as ventricular premature systole.

Since we are unable to demonstrate any value from epinephrine, and because the dangers which may result from its use are greatly increased in the obstetric conditions developing in contraction ring dystocia, we believe it unwise to use epinephrine in the management of this complication.

Conclusion

1. The human uterus can serve as a useful means of studying the action of certain drugs which have been studied on experimental animals: It is only by this means that we may avoid the pitfalls of directly transferring animal studies to the human being.

2. The action of adrenalin was studied on three types of human uteri: (a) laboring uteri with spontaneous rhythm, (b) puerperal uteri exhibiting spontaneous rhythm, and (c) puerperal uteri with an oxytocically induced rhythm.

3. Epinephrine causes a premature contraction of the uterus which is followed by a short latent period (compensatory pause) but without evidence of relaxation.

4. Any apparent relaxation which follows epinephrine is always preceded by a period of increased activity.

5. We find no evidence to support the use of epinephrine in disturbances of uterine contraction such as Bandl's ring, retraction rings, etc.

6. Because of fatigue, dehydration, and shock, epinephrine is potentially dangerous in these patients and is not recommended.

References

1. Rudolph, L.: J. Obst. & Gynaec. Brit. Emp. **42**: 992, 1935.
2. Dale, H. H., and Laidlaw, P. P.: J. Physiol. **45**: 1, 1912.
3. Gunn, J. A.: Proc. Royal Soc., London, B **87**: 551, 1913-14.
4. Rucker, M. P.: Am. J. Obst. & Gynec. **14**: 609, 1927.
5. Woodbury, R. A., Hamilton, W. F., and Torpin, R.: Am. J. Physiol. **121**: 640, 1938.
6. Ivy, A. C.: Am. J. Obst. & Gynec. **22**: 388, 1931.
7. Bourne, Aleck, and Burn, J. H.: J. Obst. & Gynaec. Brit. Emp. **34**: 249, 1927.
8. Gruber, C. M.: Endocrinology **9**: 407, 1925.
9. Rudolph, L., and Ivy, A. C.: Am. J. Obst. & Gynec. **19**: 317, 1930.
10. Sun, Ko Chi: Bull. Johns Hopkins Hosp. **36**: 280, 1925.
11. Reynolds, S. R. M.: Physiology of the Uterus, New York, 1939, Paul B. Hoeber, p. 314.
12. Williams, J. W., and Stander, J. H.: Obstetrics, ed. 8, New York, 1941, D. Appleton-Century, p. 963.
13. McGill, J. W.: Wisconsin M. J. **40**: 105, 1941.
14. Miller, E. G., Cochrill, J. R., and Kurzrok, Raphael: Am. J. Obst. & Gynec. **33**: 154, 1937.
15. Titus, Paul: The Management of Obstetric Difficulties, St. Louis, 1937, The C. V. Mosby Co., p. 385.
16. Beck, A. C.: Obstetrical Practice, Baltimore, 1935, Williams & Wilkins Co., p. 477.
17. Irving, F. C.: A Textbook of Obstetrics, New York, 1936, The Macmillan Co., p. 356.
18. Daro, A. F., Heskett, B. F., and Schiller, H. A.: J. A. M. A. **114**: 649, 1940.
19. Harer, W. B., and Sharkey, J. A.: J. A. M. A. **114**: 2289, 1940.
20. Freeman, N. E.: Am. J. Physiol. **103**: 185, 1933.
21. Cannon, W. B.: Am. J. Physiol. **50**: 399, 1919

PERIPHERAL BLOOD FLOW DURING GESTATION*

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IT IS generally accepted that the pregnant state is associated with cardiovascular changes of considerable magnitude. Obviously, since the growing embryo requires additional nourishment, and since the waste products consequent to its metabolism must be excreted, a gradually increasing burden is placed upon the maternal circulation. In 1915, Lindhart[1] found that the cardiac output in the one pregnant patient studied increased 50 per cent during gestation. This result has subsequently been confirmed by a number of investigators.[2-5] Associated with the augmented cardiac output is a definite elevation in pulse rate which tends to increase gradually until term and then falls immediately after delivery. The changes in blood pressure are not significant nor constant, although there is a tendency for a widening of the pulse pressure during the fourth to the ninth lunar months.

Besides the above changes, a number of workers[6, 7] have reported a progressive increase in plasma and total blood volume, which, according to Cohen and Thomson,[8] may well be the cause for the augmented cardiac output. The latter investigators have also confirmed the observation of Pelissier[9] that the viscosity of the blood is decreased during at least the first nine lunar months of pregnancy.

With such definite alterations in the dynamics of the circulation, it would be expected that the blood flow to the extremities is likewise affected. In this respect, Huchart[10] postulated the existence of peripheral vasoconstriction in pregnancy and for many years this idea was generally accepted. In fact, it has been considered that a circulating vasopressor substance is the responsible agent, although no definite evidence to support such a point of view has ever been presented. The velocity of the blood in pregnancy has been extensively studied,[11] most of the reported readings falling within the range of normal, nonpregnant women. However, according to Cohen and Thomson,[11d] there is a trend toward an increase up to the thirty-sixth week.

In the present investigation, the actual rate of resting peripheral blood flow was determined in a series of pregnant women, using the venous occlusion plethysmographic method.

Method

Blood flow readings were made at monthly intervals or at less during the last two trimesters of gestation and for a month or two after de-

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Presented at a meeting of the American Physiological Society, held at Boston, Mass., April, 1942.

livery. Twelve normal pregnant women and one with fully compensated mitral stenosis were utilized in the study. The rate of blood flow was determined separately in the hand, forearm and leg at a bath temperature of 32° C. (temperature of the water in the plethysmograph) and at a room temperature of 25° to 27° C., according to the technique previously described.[12] The blood pressure and pulse rate were recorded on each occasion.

Results

For comparison with the data obtained in the pregnant subjects, a series of 45 normal, nonpregnant women of approximately the same age group was used. The blood flow in the leg was found to be 1.3 c.c. per minute per 100 c.c. limb volume (σ–0.4),* in the forearm, 1.5 c.c. (σ–0.5) and in the hand, 7.2 c.c. (σ–3.1).

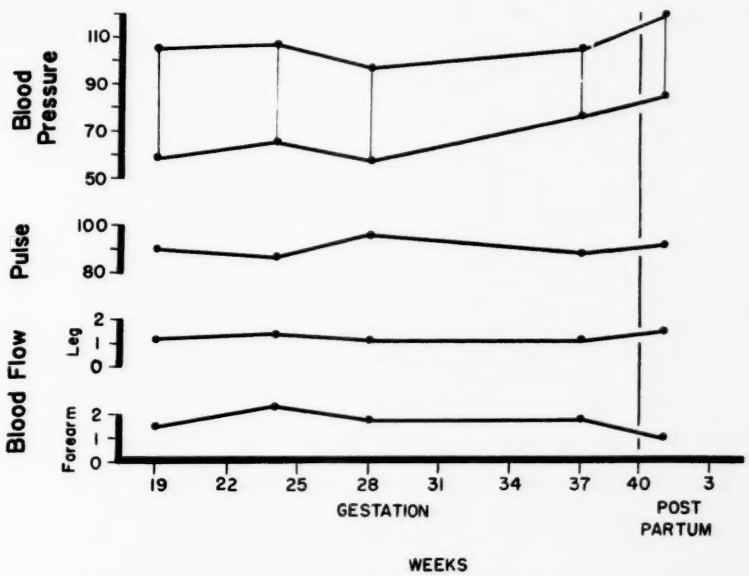

Fig. 1.—Blood flow changes in leg and forearm in Subject L.F. Readings in cubic centimeters per minutes per 100 c.c. limb volume.

Blood Flow During Gestation.—The leg was examined in 5 subjects, in each case on the average of 3 to 4 times during the period of pregnancy (Table I). In every instance the blood flow readings fell within

TABLE I. RESTING BLOOD FLOW IN THE LEG DURING AND AFTER PREGNANCY*

SUBJECT	PREGNANCY IN WEEKS								POST-PARTUM PERIOD IN WEEKS		
	17-20	20-23	23-26	26-29	29-32	32-35	35-38	38-40	0-3	3-6	6-9
F. F.							1.6	2.1			
L. L.					2.1	1.7					
L. A.			2.0	1.8		1.7					
L. C.		1.8		1.2	1.1	1.1				2.2	
L. F.	1.2		1.4	1.2			1.2		1.5		

*Blood flow in cubic centimeters per minute per 100 c.c. limb volume.

*Standard deviation.

the range of the determinations obtained in the control series (an average for the whole group of 1.6 c.c. per minute per 100 c.c. limb volume, as compared with 1.3 c.c. for the nonpregnant women). Fig. 1 is typical of the circulatory changes in the leg observed during the period of gestation. In 1 of the subjects (L. C.) there were some variations in the individual figures, but these were no more marked than those noted in the group of nonpregnant women taken at intervals over the same period of time.

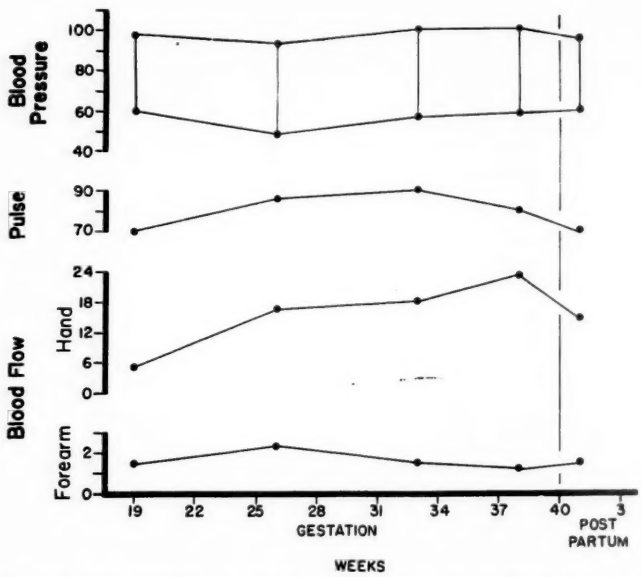

Fig. 2.—Blood flow changes in hand and forearm in Subject I.G. Readings in cubic centimeters per minute per 100 c.c. limb volume. Definite increase in blood flow observed during period of gestation, with a tendency toward a fall after delivery.

The forearm was examined in 11 subjects, and in 8 of these the readings obtained during the period of gestation again fell within the range for normal determinations (an average of 1.6 c.c. for the group, as compared with 1.5 c.c. for the normal series) (Table II). Typical responses

TABLE II. RESTING BLOOD FLOW IN FOREARM DURING AND AFTER PREGNANCY*

SUBJECT	PREGNANCY IN WEEKS								POST-PARTUM PERIOD IN WEEKS		
	17-20	20-23	23-26	26-29	29-32	32-35	35-38	38-40	0-3	3-6	6-9
F. F.							1.2	1.4			
L. L.					1.8	1.3					
B. S.					1.8		1.6		1.2		1.9
R. S.		2.2		1.4		1.9				2.4	
L. C.		1.7		2.0	1.7	2.0				1.9	
I. G.	1.5		2.3			1.5		1.3	1.5		
L. F.	1.5		2.4	1.7			1.9		1.0		
C. S.							1.6	1.1			1.9
A. G.		3.6	2.3	2.7		1.8		1.5			
H. F.			2.3	3.2					1.5		
L. A.				2.0		2.2	2.4	3.6	3.1	2.5	2.6

*Blood flow in cubic centimeters per minute per 100 c.c. limb volume.

are noted in Figs. 1 and 2. It is of interest that in the patient with compensated mitral disease (L. C., Table II) the results in the forearm and leg were similar in all respects to those already described for normal subjects.

In the remaining 3 of the 11 subjects in whom the forearm was studied, a number of the determinations obtained during the period of gestation were definitely increased (an average for all of the determinations of 2.5 c.c. as compared with 1.5 c.c. [σ–0.5]) for the nonpregnant women. No consistent trend, however, could be noted. In one instance (A. G.) the readings were initially high, to decrease as term was approached, while in another (L. A.) the reverse was true. In the case of H. F., the results were indefinite, since only two determinations could be obtained before the subject went into premature labor at the end of the thirty-eighth week of pregnancy. These patients differed in no way from the others in the group in respect to blood pressure or pulse rate changes.

The hand was repeatedly examined in 7 subjects (Table III) and in all instances a significant increase in the rate of blood flow was noted as the pregnancy advanced. This is clearly demonstrated when the average control figure of 7.2 c.c. per minute per 100 c.c. limb volume (σ–3.1) is compared with the readings obtained in the last two trimesters of gestation (Table III). Fig. 2 is typical of the increase in hand blood flow observed during the pregnant state.

TABLE III. RESTING BLOOD FLOW IN THE HAND DURING AND AFTER PREGNANCY*

SUBJECT	PREGNANCY IN WEEKS								POST-PARTUM PERIOD IN WEEKS		
	17-20	20-23	23-26	26-29	29-32	32-35	35-38	38-40	0-3	3-6	6-9
B. S.							11.7		8.3		4.2
L. A.							21.3	15.8	26.3	9.7	14.0
I. G.	5.1		16.8			18.0		23.8	14.2		
A. G.		10.0		14.3		16.8		18.2			
C. S.							9.1	10.6			10.4
R. S.		5.4		12.4		25.4				7.7	
H. F.		9.8		15.6					23.2		

*Blood flow in cubic centimeters per minute per 100 c.c. limb volume.

Blood Flow in the Post-Partum Period.—It was not possible to obtain readings on all of our subjects following delivery, but sufficient data were accumulated to warrant drawing certain conclusions. In all instances in which the rate of blood flow in the forearm and leg remained within the normal range during the pregnant state, no significant change occurred in the post-partum period (Tables I to III, Figs. 1 and 2). In the case of the three subjects in whom an increased forearm blood flow had been noted during gestation, normal readings were observed after delivery. In respect to the hand, the fall in blood flow was not always observed immediately, the figures remaining elevated in a number of the cases for some time afterwards. The first set of results obtained in the post-partum period for L. A. and H. F. cannot be considered to be uncomplicated readings, since the tests were performed at the time of onset of lactation.

Blood Pressure and Pulse Rate Changes During and After Gestation.—The blood pressure readings in the series did not vary significantly during the period of pregnancy (Figs. 1 and 2). In 3 instances there was

a slight decrease in pulse pressure as a result of a similar alteration in the systolic blood pressure level, the diastolic pressure for the most part remaining unchanged. With respect to the pulse rate, the readings were generally higher than normal, with a tendency toward a fall either in the last months of pregnancy or in the post-partum period (Figs. 1 and 2).

Discussion

From the foregoing, it is clear that the changes in the local circulation through the forearm and leg in gestation are for the most part negligible, despite significant alterations in the general hemodynamics. Certainly the hypothesis that there is a vasoconstriction of the blood vessels in the extremities in this state is not supported by our findings. In view of the increased cardiac output, one might theoretically have expected an augmentation of peripheral blood flow, but, with the exception of 3 cases, this was not apparent in the forearm or leg. Evidently, then, the increased quantity of blood ejected by the heart is utilized in the main in satisfying the greater requirements of the uterine circulation; little, if any, selective shunting of blood from the extremities to the placenta taking place.

It is of interest to note that despite the consistent finding of an elevated venous pressure in the lower extremities in pregnancy, in consequence of the increased resistance to venous return by the enlarging uterus,[5, 13] the rate of blood flow in the leg remains normal. This is further proof for the view that changes in the venous side of the circulation, unless marked, do not necessarily affect arterial inflow.

The results in the hand merit further discussion. It appears quite probable, on the basis of our data, that there is a definite trend toward an increase in the rate of blood flow through this vascular bed as the pregnancy progresses. Since the hand ordinarily plays an important role in body heat conservation and dissipation, it was at first considered that the altered maternal circulation through this site was a manifestation of the mechanism whereby the heat produced by the metabolic processes in the fetus is removed. However, the fact that in a number of subjects the rate of blood flow in the hand did not diminish in the period immediately following parturition would be opposed to this view. Another explanation may be related to the observation that in pregnancy there is an increase in oxygen consumption, which is greater than that expected on the basis of the sum of the high metabolic rate of the fetus and the augmented maternal respiratory work.[14] It is possible, therefore, that an overfunction of the thyroid gland[14] might be the explanation for the high blood flow in the hand. It is of interest that all of the women in the series volunteered the information that, except for the first few months, their hands and feet had become very much warmer during gestation. In 9 of these cases the extremities were ordinarily quite cold. Since all of our studies were made during the

winter months, the high blood flow in the hand is of significance, for under such circumstances it could not have been due to the external temperature.

Summary and Conclusions

The resting peripheral circulation was investigated in 13 women, first in the pregnant state and then during the post-partum period. By means of the venous occlusion plethysmographic method, the rates of blood flow in the hand, forearm and leg were studied separately.

It was found that in the majority of the cases the blood flow in the leg and forearm remained within normal limits during at least the last two trimesters of gestation, while in the hand there was a definite trend toward an increase in circulation. In no instance was a decrease in the rate of blood flow observed in either the forearm, leg or hand.

It is concluded that the increased uterine circulation during gestation is obtained primarily through the mechanism of an augmented cardiac output and not at all at the expense of the blood flow to the extremities.

Valuable technical assistance was contributed by Mrs. W. Littleford.

References

1. Lindhart, J.: Arch. f. d. ges. Physiol. **161**: 233, 1915.
2. Weiss, R.: Klin. Wchnschr. **3**: 106, 1924.
3. Gammeltoft, S. A.: Surg., Gynec. & Obst. **46**: 382, 1928.
4. Stander, H. J., and Cadden, J. F.: Am. J. Obst. & Gynec. **24**: 13, 1932.
5. Burwell, C. S., Strayhorn, W. D., Flickinger, D., Corlette, M. B., Bowerman, E. P., and Kennedy, J. A.: Arch. Int. Med. **62**: 979, 1938.
6. Thomson, K. J., Hirsheimer, A., Gibson, J. G., II, and Evans, W. A., Jr.: Am. J. Obst. & Gynec. **36**: 48, 1938.
7. Dieckmann, W. J., and Wegner, C. R.: Arch. Int. Med. **53**: 71, 1934.
8. Cohen, M. E., and Thomson, K. J.: J. A. M. A. **112**: 1556, 1939.
9. Pelissier, M. P.: Arch. mens. d'obst. et de gynéc. **2**: 306, 1912.
10. Huchart, H.: Maladies du coeur, artériosclérose, Paris, 1910, J. B. Bailliére et fils.
11. a. Klee, F.: Ztschr. f. Geburtsh. u. Gynäk. **88**: 308, 1924.
    b. Spitzer, W.: Arch. f. Gynäk. **154**: 449, 1933.
    c. Greenstein, N. M., and Clahr, J.: Am. J. Obst. & Gynec. **33**: 414, 1937.
    d. Cohen, M. E., and Thomson, K. F.: J. Clin. Invest. **15**: 607, 1936.
12. a. Abramson, D. I., Zazeela, H., and Marrus, J.: Am. Heart J. **17**: 194, 1939.
    b. Ferris, E. B., Jr., and Abramson, D. I.: Ibid. **19**: 233, 1940.
13. Burwell, C. S.: Tr. A. Am. Physicians **52**: 289, 1937.
14. Jensen, J.: The Heart in Pregnancy, St. Louis, Mo., 1938, The C. V. Mosby Co.

THE PROBLEM OF ABORTION*

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THAT the problem of abortion is one of progressively increasing importance is evidenced by the fact that its incidence has increased by an appalling percentage during the last several decades. This is particularly true of induced abortion. Taussig,[1] in his book on the subject, estimates that the ratio between abortions and confinements is 1:2.5. In itself this would not be alarming were it not for the fact that the mortality rate in a most conservative estimate is 1.2 per cent throughout the country. Interpreted statistically, of the estimated 680,000 abortions in the United States in 1941, at least 8,200 terminated fatally. This is a figure which approximates the maternal mortality associated with term-confinements. The relatively recent increase in the prevalence of abortion is attributable in large part to certain social factors: The dishonorable stigma accompanying illegitimacy, the attempt to escape the responsibilities of parenthood, the poverty and squalor attendant upon the depression of the last ten years, the desire to raise the economic level of living by restricting the size of families, by methods most reckless and foolhardy if need be, the migration to the attractions of the cities, and in general the desertion of idealism in favor of a more secularized philosophy, especially manifest since World War I, are all contributory factors. It is the momentous significance of the problem that suggested this study by several of us at the Milwaukee County Hospital.

Material

Herewith are reviewed 800 consecutive abortions, a series which includes all the abortions of every type treated in this Hospital during the years 1937, 1938, 1939, 1940, and the first three months of 1941. To avoid confusion, a brief review of the definition of terms accepted on our service is included.

In its most exacting definition, abortion includes all cases where detachment or expulsion of the fertilized ovum occurs before viability,[1] i.e., twenty-six to twenty-eight weeks. However, for the sake of convenience, this series includes only those cases where pregnancy was terminated before the fifth month; pregnancies beyond this period are treated on the obstetric rather than on the gynecologic service. This differentiation is made since Wisconsin state laws require neither a birth certificate nor a death certificate unless the gestation has proceeded beyond five months or twenty weeks.

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In threatened abortion, which is characterized by uterine contractions and a bloody show, the ovisac itself has not yet been detached. Incomplete abortion is the more advanced stage, in which portions of the products of conception are expelled and the remainder are retained within the uterus. On the other hand, in complete abortion all the gestational products have been expelled. Spontaneous abortion is one initiated by intrinsic causes, in contrast to induced abortion, in which external factors are responsible. The induced or illegal abortion as it is sometimes termed, may have been perpetrated either by the patient herself, the so-called self-induced abortion, or by a second party, the so-called criminally-induced abortion. In a missed abortion, the pregnancy is retained intact for longer than two months after the death of the fetus.

We have subdivided all abortions further into febrile and afebrile groups, arbitrarily defining the febrile or septic patient as one in whom the temperature has risen to 100.4° F. on any two hospital days excepting the day of admission. The exclusion of the day-of-admission temperature is made because of the inexplicable occurrence of a low-grade fever in a large percentage of patients at the time of their entry into the hospital which subsides without treatment or recurrence shortly thereafter.

TABLE I. INCIDENCE

1937	182
1938	296
1939	150
1940	141
1941 (first four months)	31
Total	800

Table I shows the comparative incidence of abortions in the last four years. We cannot account for the increased incidence in 1938.

TABLE II. COMPARATIVE INCIDENCE

Spontaneous abortion (Including 76 which were admitted as threatened but went through the inevitable stage to completion, and including 6 hydatid moles)	553
Self-induced abortion	123
Threatened abortion, treatment successful	91
Criminally-induced abortion	27
Missed abortion	6
Total	800

Spontaneous

Of the 553 spontaneous abortions, only 53, or 10 per cent, were febrile; whereas 57, or approximately 50 per cent, of the 123 self-induced abortions were febrile, and 11, or roughly 40 per cent, of the 27 criminal abortions were septic. In other words, the incidence of infection is four to five times as great if the pregnancy has been tampered with by outside interference. Our statistics show further that age is not a factor in the incidence of spontaneous abortions, since all age groups were represented in a ratio directly proportional to the fertility age of women. As one would expect, social status or religious affiliation has no effect

on the incidence of spontaneous abortion. Judging from our figures, one would be inclined to believe that the white race is less susceptible to spontaneous abortion than is the Negro race, since 43 of this group were colored, a figure not in proportion to the Negro census in this Hospital. Syphilis is no longer considered an important etiologic factor responsible for early spontaneous abortion; in fact, only 14 women in this large group had positive Wassermann reactions. Occasionally one hears the remark that first pregnancies are more likely to terminate in spontaneous abortion than are subsequent gestations. This statement is not confirmed by our data, since the incidence is practically the same in women who are pregnant for the first, second, third, or fourth time. The sharp decline in the occurrence beyond this number of gravidity can be explained by the fact that relatively few women have more than four children.

TABLE III. COMPARATIVE INCIDENCE OF ABORTION IN RELATION TO AGE

TYPE	AGE							
	15-20	20-25	25-30	30-35	35-40	40-45	45-50	TOTAL
Spontaneous	43	139	148	104	75	41	3	553
Self-induced	7	32	37	25	17	4	1	123
Criminally induced	3	9	10	1	4	--	--	27

For the most part, all age groups are affected in a ratio directly proportional to the fertility age of women.

TABLE IV. COMPARATIVE INCIDENCE OF ABORTION IN RELATION TO GRAVIDITY

TYPE	GRAVIDITY								
	I	II	III	IV	V	VI	VII	VIII AND UP	TOTAL
Spontaneous	75	90	86	78	47	47	41	89	553
Self-induced	17	17	26	20	10	16	3	14	123
Criminally induced	11	5	2	5	3	--	--	1	27

TABLE V.

TERM OF GESTATION	NO.
One month pregnant	75
Two months pregnant	207
Three months pregnant	161
Four months pregnant	110
Missed abortion	6

The highest incidence of spontaneous abortion occurs in the second month of gestation. An interesting observation was the high incidence of previous pelvic surgery in the women who experienced spontaneous abortions. Seventy-one women in this group had already been subjected to surgery of one type or another on their internal generative organs.

Among the more serious medical complications with which this group of women was afflicted are those given in Table VI.

In only 125, or less than one-fourth, was there evidence that all the products of conception definitely had been expelled or delivered either prior to admission or on entry into the hospital so that a diagnosis of complete abortion was justifiable.

In noninfected spontaneous abortions, severe anemia is not common. A leucocyte count above 15,000 is the exception and a sedimentation

TABLE VI. COMPLICATIONS

Rheumatic heart disease	8
Hyperthyroidism	8
Pulmonary tuberculosis	7
Chronic nephritis	7
Diabetes mellitus	3
Hypothyroidism	2
Thyrotoxic heart disease (decomp.)	1
Congenital heart disease (decomp.)	1
Hypertensive heart disease (decomp.)	1
Acute agranulocytosis	1
Scarlet fever	1
Carcinoma of breast	1
Carcinoma of cervix	1

rate above 100 mm. precipitation (Westergren) is a rarity. For that matter, there was surprisingly little difference between the laboratory findings in the infected and those in the noninfected spontaneous abortions.

The key to our treatment of abortion revolves around the word "conservatism." This is made possible by the fact that in a charity institution cost of care is not a pressing problem. It is admitted, however, that in private practice, where the patient is paying for each hour's stay in the hospital, such conservatism is not entirely feasible, and that immediate evacuation of the uterus upon making a diagnosis of inevitable or incomplete abortion in the absence of sepsis, may expedite recovery in selected cases.

The method of management of our cases is essentially as follows: Immediately upon admission, a careful sterile vaginal and speculum examination is made for the purpose of both diagnosis and treatment. Any tissue palpable or visible within the vaginal or cervical canals is removed with a sterile ovum forceps, the uterine cavity itself not being invaded.

Specimens of all tissue removed are examined by the pathologist. A microscopic study verifies the diagnosis, and his report has been found invaluable on many occasions as the only tangible evidence for medicolegal testimony. An oxytocic, either pituitrin or ergotrate, is then administered. If all the products of conception have been discharged from the uterus, bleeding will have ceased. If, on the other hand, any tissue remains, bleeding will continue. In the latter instance, a pack saturated with a 5 per cent aqueous solution of mercurochrome is inserted into the external os of the cervix and vagina. The pack is removed within twelve to twenty-four hours and not infrequently the remainder of the products of conception will be found then lying free and accessible. We hesitate about packing the infected uterus and strenuously emphasize against permitting a pack to remain more than six hours in the presence of fever. To hasten involution, a course of oxytocics, usually consisting of ergotrate gr. $\frac{1}{320}$ every four hours for six doses, each dose being accompanied by quinine sulfate gr. ii, is given. The patient is subjected to a dilatation and curettage only if, after three to five days, uterine bleeding is more profuse than a normal lochia. Except in those instances where hemorrhage is brisk and the bleeding

in itself absolutely necessitates the procedure, invasion of the infected uterus is considered unjustified.

Of the 553 spontaneous abortions, 481 patients received one or more courses of oxytocics; in 181 cases, a pack was inserted; only 27 of the women required one or more transfusions; and in only 120 cases, or approximately one-fifth of the total, was dilatation and curettage performed because evidence existed demonstrating that the uterus (after a conservative period of three or more days) still contained some fetal or placental elements.

The average hospital stay for the patients so treated was 7.6 days, the shortest one day, the longest thirty-nine days. Thirteen patients were curetted immediately on admission to the hospital; their average stay was 9.4 days. The treatment of the 53 infected spontaneous abortions consisted essentially of oxytocics, repeated transfusions of whole blood, and sulfanilamide or its derivatives since it became available on our service in 1938. Eight of these patients were curetted only after a reasonable period of normal temperatures permitted. The average hospital stay for the septic spontaneous abortions was 15.8 days; the average number of days morbidity was 4.8. There were no deaths in the entire series of spontaneous abortions.

Threatened Abortion

Here treatment has been quite discouraging. Of the 167 cases that were diagnosed as threatened abortion on admission, only 91 were discharged with the pregnancy supposedly salvaged. The remaining 76 continued on through the inevitable stage into either an incomplete or complete abortion. We do not attempt to excuse these unfavorable results by explaining that in many instances the patient had so long neglected her symptoms of bleeding and pain that when she finally sought medical attention in the hospital, the abortion should have been classified on admission as inevitable rather than threatened. Having made use of all of the suggested medications, beginning with the opiates, through the barbiturates, atropine, thyroid extract, wheat germ oil, corpus luteum, up to the most recently advocated progesterone, our results would seem to indicate that if a blighted ovum of defective germ-plasm is growing, nature will empty the uterus regardless of any measures which might temporarily inhibit uterine contractions. However, since one cannot determine objectively in which cases a healthy trophoblast is developing, all measures possible should be instituted to maintain the uterus in a state of quiescence until the disturbing factor is eradicated. Our statistics indicate that treatment of threatened abortion is more successful if the gestation has advanced beyond the first month, since we were able to save only three cases in which the patient had missed but one menstrual period and the Friedman test had verified the diagnosis of pregnancy. The fact that in every threatened abortion that we were able to save, the erythrocyte count was above three million, would tend to substantiate the contention that severe anemias predispose to abortion. Furthermore, we are satisfied in our own minds that a uterus once infected cannot and will not retain the pregnancy, for in not a single instance were we able successfully to prevent an infected uterus from emptying its contents.

Self-Induced Abortion

All kinds of devices were admittedly employed in this group of cases. The remarkable ability of the uterus to limit infection is evidenced by the fact that only 57 of the 123 self-induced abortions became septic. This entire series included but three negresses. Thirty-seven of this group became pregnant out of wedlock. Gravidity and parity play no part in this story. Only twelve had missed but one menstrual period; the remainder, apparently hoping the amenorrhea was due to some other factor, waited two or more months before they attempted interference. That the uterus is reluctant about relinquishing a healthy pregnancy is shown by the fact that only 18 of this entire series of 123 self-induced abortions were complete. Here, too, the management of these cases, either infected or not, was conservative. The average hospital stay for the afebrile group was eight days. In the infected group, the average number of days of morbidity was 6.5 and the average number of hospital days was 15.7. Three of these women with self-induced abortion died.

Criminal Abortions

As previously mentioned, there were 27 instances in which criminal induction was confessed. In all of these, an instrument was used In 8, a physician was responsible; in 10, a midwife; and in the remainder, the accomplice was listed as "a friend." There were no colored women in this series. Sixteen, or more than half, were either single, divorced, or widowed, obvious instances in which the social stigmas of illegitimate pregnancy prompted their course. Strangely enough, only 4 had been emptied completely. Eleven of the criminal abortions were septic. There was one death in this group.

Summary and Conclusions

Although in this entire collection of 800 abortions, there were only four deaths, yet more noteworthy is the fact that not a single death occurred in the last 557 cases of the series. That an element of good fortune was present is admitted, although many of the women entered the hospital in critical condition due either to exsanguination or sepsis or a combination of both; none were in actual extremis. However, there are several points in the modern mode of treatment that deserve attention. The practice of conservatism has been emphasized sufficiently. The administration of oxytocics, by provoking contraction of a sluggish myometrium, serves a dual purpose. Not only are avenues for extension of bacterial invasion through the uterine wall closed, but, by stimulating expulsion of necrotic debris from within the uterine cavity, the nidus of the contaminating saprophytes is eliminated. The judicious use of sulfanilamide and more recently of sulfapyridine and sulfathiazole, particularly against the hemolytic streptococcus, is now clinically well established, and we are certain that they have been responsible agents for lowering the morbidity and mortality rate since their introduction into our therapeutic armamentarium in 1938. Because the number of cases in which scarlet fever convalescent serum

was used is small, we cannot accurately evaluate its merits. Without a doubt, the greatest share of credit belongs to the most efficacious therapeutic agent we have at our disposal, namely, transfusions of whole blood. Infections attributable to the anaerobic streptococcus are characterized by an anemia due in large part to the proteolytic action of the organism on erythrocytes and certain strains of this organism are notoriously resistant to chemotherapy. Whole blood, then, not only compensates for the blood loss due to the hemorrhage which characterizes neglected abortions, but also combats the anemia due to the bacterial hemolysis. Its polyvalent effect goes further, for not only is it beneficial as a supportive measure, as physiologic nourishment and to counteract dehydration, but its bactericidal effect is reflected by an immediate elevation of the phagocytic titer of the patient's blood. For the anemic, infected postabortal patient, the administration of repeated small transfusions, 250 to 500 c.c. of whole blood daily or on alternate days, is strenuously advocated.

References

1. Taussig, F. J.: Abortion, 1936, St. Louis, The C. V. Mosby Co.
2. Cron, Roland S., and Lahmann, Albert H.: Wisconsin M. J. **39**: 327, 1935.

THE PROBLEM OF UNSUSPECTED TUBERCULOSIS DURING PREGNANCY IN THE NEGRO

Incidence by Roentgenologic Techniques in 1,000 Consecutive Cases

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EISELE and associates[1] have in this JOURNAL recently again called attention to the importance of the problem of the unsuspected cases of clinically important pulmonary tuberculosis among any series of prenatal patients. They have presented data on the examination of 10,968 pregnant white women by fluoroscopy and x-ray at the Chicago Lying-in Hospital. Examination demonstrated an incidence of 1.0 per cent clinically important tuberculosis as found by this method, to be contrasted with a discovered incidence less than one-tenth as great when no roentgenologic technique is employed for the detection of the disease.

Eisele and associates give figures for the incidence of tuberculosis in a white prenatal group, and in an institution exclusively for the care of obstetric and gynecologic problems, in a large metropolitan area. Various studies have shown that the incidence of tuberculosis will vary with the definition of the particular group investigated. It will therefore be of interest to compare with Eisele's figures the findings, accord-

ing to an identical method of examination, in a group of Negro prenatal patients, in the same city, at the Provident Hospital and Training School, an institution which gives general medical care to the large Negro population of Chicago.

Bloch and associates[2] have made a preliminary report on an investigation of the incidence of tuberculosis and other chest pathology among clinic patients of the Out-Patient Department of Provident Hospital, in a study begun in November, 1939. A fluoroscopic unit was installed as an integral part of the admitting routine of that Department, and all patients have had a chest fluoroscopy in addition to other routine laboratory investigations since that time. When definite or suspected lesions of clinical importance are seen on fluoroscopy, an x-ray of the chest is ordered, and it was their experience that about 7 per cent x-rays were ordered, about half of which showed definite pulmonary tuberculous pathology. The results to be presented here are those of the examinations of 1,000 consecutive patients attending the Pre-Natal Clinic of Provident Hospital, from November, 1939, to May, 1942, a group easily separated from the total number of out-patients so examined.

Material and Results

The patients attending the prenatal clinic are all of the Negro race. The vast majority are of the lower economic strata, and few are able to pay the full cost of their obstetric care. For the year 1941 of 131,379 visits to the Out-Patient Department of Provident Hospital only 5,323 (4.1 per cent) were pay visits, the remainder (95.9 per cent) free or relief agency cases. For 1940 the figures were practically identical. Approximately the same proportions apply to the women seen in the prenatal clinic. Provident Hospital is the only exclusively Negro hospital in Chicago to serve a population of approximately 300,000 Negroes. Most of the prenatal patients seen at Provident Hospital are cared for during the early months of their pregnancy at the dispensaries of the City of Chicago Health Department, and report to Provident for prenatal care and delivery only in the last trimester. This results in prenatal patients being seen at Provident later during gestation than in most prenatal clinics, the distribution at Provident contrasting with that at the Chicago Lying-in Hospital clinic, as reported by Eisele,[1] as shown in Table I.

TABLE I

GROUP	PER CENT EXAMINED IN		
	FIRST TRIMESTER	SECOND TRIMESTER	THIRD TRIMESTER
Provident Hospital	8.5	37.1	54.4
Chicago Lying-in Hospital	37.9	42.1	20.0

The average woman reported to Provident Hospital for her initial prenatal examination and fluoroscopy when she was 6.42 months pregnant; the average woman at Lying-in Hospital was 4.53 months. As in the case of Eisele's figures for Lying-in Hospital, at Provident there was a slight tendency for those women found to have clinically important tuberculosis to report for their initial examination somewhat later than the average of the total group of prenatal patients. This inability to diagnoses clinically important tuberculosis sufficiently early during

gestation complicates the problem of adequate care for the patient, as usually the diagnosis is made too late to carry out safely a therapeutic abortion where such a procedure is indicated. The distribution of the stage of gestation at the time of the first examination at Provident Hospital contrasted with that at Lying-in Hospital, is shown graphically in Fig. 1.

For reasons largely sociologic Negro women tend to become pregnant somewhat earlier than white women, and to continue bearing children longer. At Provident Hospital, including all multiparas with primiparas, the average age of prenatal patients was 24.2 years; at Chicago Lying-in Hospital the similar average reported by Eisele[1] was 25.8 years. The distribution of pregnant women by age groups in the two institutions is compared in Table II.

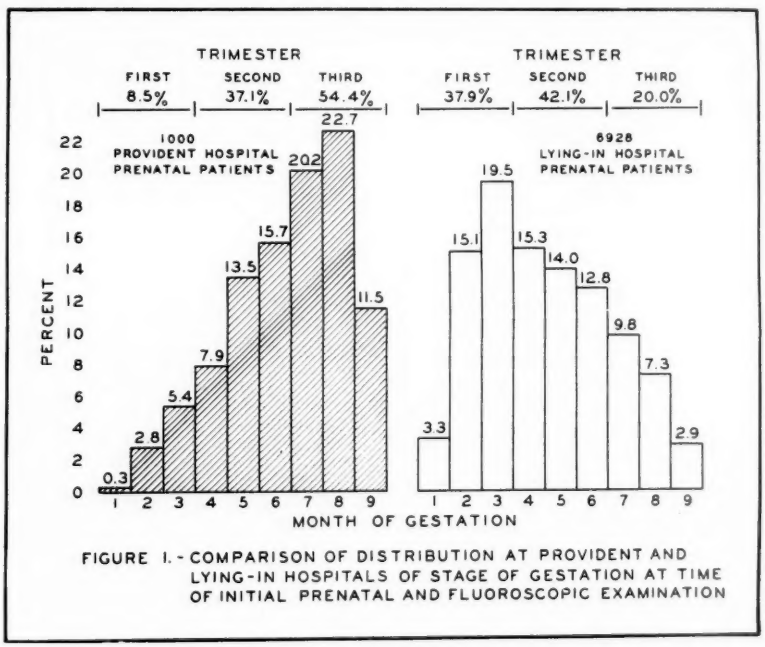

Fig. 1.—Comparison of distribution at Provident and Lying-in Hospitals of stage of gestation at time of initial prenatal and fluoroscopic examination.

Thus it is seen that the average Negro prenatal patient seen at Provident Hospital is slightly younger than the average prenatal patient at Lying-in Hospital, is seen at a somewhat later stage in gestation, and is of a somewhat lower economic group.

These differences may serve to account for the different incidence noted at Provident Hospital. Among the 1,000 consecutive prenatal patients examined over a thirty-month period, 18 cases of clinically im-

TABLE II

AGE GROUP	PER CENT IN AGE GROUP	
	LYING-IN HOSPITAL	PROVIDENT HOSPITAL
13-19	9.6	32.7
20-29	67.2	44.6
30 and over	23.2	22.7

portant tuberculosis were found, an incidence of 1.8 per cent, nearly twice the incidence at Lying-in Hospital; and 11 further cases of inactive, clinically unimportant tuberculosis, aside from calcifications of primary lesions, were discovered, a total of 29 cases, 2.9 per cent, of pulmonary tuberculosis of the reinfection type. Cases classified as clinically important included those definitely active with symptoms, and those without symptoms in whom the lesions did not demonstrate by x-ray sufficient evidence of healing by fibrosis and calcification. Cases classified as clinically unimportant were those in which such satisfactory evidence of healing by x-ray was present. In some cases observation of at least a year was necessary to classify the tuberculous lesion accurately. All 18 cases of clinically important tuberculosis were unsuspected, in the sense that they were not previously known to have such disease; and all were considered active, although most did not have symptoms when first seen. The incidence of reinfection tuberculosis by age groups is given in Table III.

TABLE III. INCIDENCE OF PULMONARY TUBERCULOSIS IN 1,000 PRENATAL NEGRO PATIENTS DISCOVERED BY ROUTINE FLUOROSCOPY, PROVIDENT HOSPITAL

AGE RANGE	TOTAL NO. IN AGE RANGE	CLINICALLY IMPORTANT TUBERCULOSIS		CLINICALLY IMPORTANT AND UNIMPORTANT TUBERCULOSIS	
		NO.	PER CENT	NO.	PER CENT
13-19	327	6	1.8	10	3.0
20-29	446	9	2.0	13	2.9
30 and over	227	3	1.3	6	2.6
Totals	1000	18	1.8	29	2.9

Average age 1,000 women at time of fluoroscopy, 24.2 years.

The study of the incidence of tuberculosis among prenatal patients at Provident Hospital affords an opportunity to compare it with the incidence of tuberculosis among other nonpregnant Negro women, of the same age groups drawn from the same general population, an opportunity not afforded by the study of Eisele and associates at the Lying-in Hospital. In women of the childbearing age the figures for the total group examined at Provident Hospital[3] are: clinically important tuberculosis, 2.1 per cent, both clinically important and clinically unimportant tuberculosis, 3.2 per cent. The comparable figures for the prenatal group, 1.8 per cent and 2.9 per cent, respectively, are slightly but not significantly lower. It therefore would appear that prenatal patients at Provident Hospital have approximately the same incidence of tuberculosis as other women of the same age group coming to the same clinic.

Discussion

Edwards[4] has presented figures which indicate that the lower the economic status of the group studied by x-rays, the higher in general the incidence of clinically important tuberculosis found. His figures do not indicate a significant difference in the incidence in Negroes and in whites. Others[5] have reported the same experience. Edwards' figures, and those of Bloch and associates[2] indicate a slight increase in

incidence with increasing age, but a study of the incidence of all women in the total group studied at Provident Hospital[3] does not indicate such a significant rise with age in women, although there is an increase with age in the men examined. The difference in age between the two prenatal groups, at Lying-in and Provident Hospitals, is slight. If Edwards is correct that there is not a significant difference on the basis of race, it would therefore appear that the noted difference in the incidence in the two institutions is probably on the basis of economic and other sociologic factors.

It is not the purpose of this report to discuss the relative merits of different methods of case-finding in tuberculosis. These have been amply stated by Eisele and associates,[1] who conclude that routine chest roentgenologic examinations are indispensable for detecting unsuspected tuberculosis in a prenatal population. The incidence of 1.8 per cent of clinically important pulmonary tuberculosis at Provident Hospital merely confirms and strengthens their contention that "tuberculosis in pregnant women is still an important problem, for although it has declined from first to seventh place as a cause of death in the general population, it still remains as the leading cause of death for women of the childbearing age." This is especially true in the case of Negro prenatal patients, for whereas the incidence of tuberculosis may not be greater in the Negro than in the white, the disease once of clinical importance tends to run a more unfavorable course in the Negro, and the mortality rate is from 3 to 4 times as high in the Negro as in the white, with a still higher ratio in the Northern states.[5]

It is not the intention of this report to offer a follow-up of the 18 cases of clinically important tuberculosis discovered by routine fluoroscopy and x-ray. A few case histories, however, will illustrate in a concrete fashion the problem of unsuspected pulmonary tuberculosis in a Negro pregnant woman, as it affects her health after delivery. Some of the more advanced cases, all with pulmonary tuberculosis not suspected prior to the initial fluoroscopic examination, have been selected for illustration, and demonstrate the seriousness of the problem. Other less extensive cases, all nevertheless active, naturally have had more favorable outcomes than these, but in every case the detection of the unsuspected pulmonary involvement has been a factor complicating the normal pre- and postnatal course.

CASE 1.—G. T., aged 18, gravida i, para 0, first visit to Prenatal Clinic Jan. 22, 1940, gestation 7½ months. Fluoroscopy January 22 showed bilateral upper lobe tuberculosis. X-ray same day confirmed diagnosis of moderately advanced bilateral apical and subapical productive tuberculosis, with no evidence of cavitation. Only complaint that of a "cold" for three weeks; no history of tuberculosis contact in family or elsewhere. Four family contacts, mother and three sisters, fluoroscoped as contacts, all negative. Raising no sputum, none obtained for microscopic examination. Wassermann and Kahn, and urinalysis

negative, blood counts normal. Sedimentation rate 11 mm. in thirty minutes, 18 in sixty minutes (Cutler). Admitted to Provident Hospital Feb. 23, 1940, normal girl born March 1 after episiotomy, usual repair. Fever of 99.6° to 100.0° F. from March 4 to 18, when patient left hospital. Repeat x-rays of chest on February 29 and March 13 showed unfavorable progress of tuberculous lesions. Attempts were made to arrange for sanatorium care elsewhere but patient and family were uncooperative. Patient became more acutely ill at home and was admitted to Cook County Hospital on May 23, 1940, and died there of advanced tuberculosis on Aug. 29, 1940, seven months after initial examination and six months after delivery.

CASE 2.—D. M., aged 17, gravida ii, para i, reported to Prenatal Clinic Feb. 5, 1940, gestation six months. Previous pregnancy terminated April 25, 1939, normally except for first degree perineal laceration, with usual repair. Infant died at four days, cause unknown. Mother was found to have active tuberculosis, and patient was x-rayed as contact of her mother by Chicago Municipal Tuberculosis Sanitarium Dispensary on Aug. 22, 1939, but no definite tuberculosis was found at that time. Fluoroscopy at Provident Hospital at time of first prenatal visit, Feb. 5, 1940, showed minimal bilateral upper lobe exudative tuberculous lesions. Past history at Provident Hospital irrelevant: infected adenoids in January, 1937; skin infection of foot, June, 1938; laceration of scalp, December, 1938. Patient uncooperative, persuaded with difficulty to return to hospital on March 3, 1940, for chest x-ray which confirmed fluoroscopic impression of minimal predominantly exudative bilateral apical and subapical tuberculosis without cavitation; and to Chest Clinic on April 2, 1940. Patient denied all symptoms, physical examination of chest was negative. Wassermann and Kahn, and urinalysis negative; blood counts normal. Admitted to Provident Hospital May 12, 1940; delivered a normal 9 pound male same day, with second degree perineal laceration, usual repair. No post-partum complications. Repeat x-ray of chest May 15, 1940, showed no change in pulmonary lesions. No sputum available for examination. Seen again in Chest Clinic June 11, no change. Sanatorium care nevertheless recommended, but patient and family uncooperative. In May, 1940, patient was in Cook County Hospital for a short time but left against advice. In August, 1940, it was learned patient had returned to work, but by March, 1941, she was much worse and reported to the Kenwood Dispensary of the Municipal Tuberculosis Sanatorium, where artificial pneumothorax was begun. Soon afterwards she was admitted to the sanatorium, but in spite of the pneumothorax and sanatorium care the tuberculosis steadily progressed unfavorably, and patient died of advanced tuberculosis there on Nov. 28, 1941, 22 months after initial examination; 18½ months after delivery.

CASE 3.—R. J., aged 26, gravida iii, para ii, reported to Prenatal Clinic Jan. 16, 1941, gestation four months. Two previous pregnancies terminated normally in 1934 and 1935, without complications, both children living and well. Fluoroscopy at Provident Hospital on Jan. 9, 1941, one week prior to prenatal visit, and chest x-ray January 11 showed minimal bilateral apical predominantly exudative tuberculosis. Repeat x-ray February 3 confirmed these findings. Seen in Chest Clinic Jan. 21, 1941, no complaints except loss of 7 pounds in weight in two

months. No tuberculous contact history. Husband and two sons, fluoroscoped as contacts, negative. Physical examination showed breath sounds slightly decreased in right upper lung field; no râles. Sputum positive for tubercle bacilli twice, negative once, in February, 1941. Wassermann and Kahn, and urinalysis negative; blood counts normal. Was referred to and hospitalized in Municipal Tuberculosis Sanitarium on March 7, 1941; delivered there in July; artificial pneumothorax on right begun soon afterwards; discharged from sanatorium Jan. 16, 1942. Seen again in Chest Clinic, Provident Hospital, Feb. 24, 1942, symptom free; sputum negative. X-ray showed approximately 40 per cent collapse of right lung, left apical lesion doing well. Patient has since gained about 25 pounds in weight, is clinically doing well, is continuing to receive artificial pneumothorax therapy, 250 to 300 c.c. weekly.

CASE 4.—L. M., aged 20, gravida i, para 0, referred by Mercy Free Dispensary to Provident Hospital, first seen at Provident in Prenatal Clinic on May 29, 1941; gestation nine months. Fluoroscopy and chest x-ray same day revealed moderately advanced exudative tuberculosis of the right upper lobe. Admitted to Provident Hospital afternoon of same day in labor, delivered normally that evening with episiotomy and usual repair. No chest symptoms, no tuberculous contact history. Mother fluoroscoped as contact, negative. Physical examination revealed slightly harshened breath sounds in right upper lung field; no râles. Left hospital, after normal post-partum course, on June 9, 1941. Sanatorium care advised but rejected. Seen in Chest Clinic at intervals from July to November, 1941, at first with no chest symptoms or altered physical findings. Wassermann and Kahn, and urinalysis negative; blood counts normal. In October patient developed cough and sputum, and râles appeared in right upper lung field. Efforts to get repeat x-ray of chest were unavailing until November 4, when film showed unfavorable progress, with more extensive lesions in upper one-fourth of right lung field, and a cavity in the lower portion of the involved area. Sputum examined 8 times, negative 7 times June to October, positive once, in November. In spite of persistent uncooperative attitude patient finally was hospitalized in Cook County Hospital on Jan. 14, 1942, but left against advice in May, 1942, and died at home one week later of advanced pulmonary tuberculosis, twelve months after initial examination and delivery.

Summary

1. One thousand consecutive patients attending the Prenatal Clinic of the Provident Hospital and Training School were examined for pulmonary tuberculosis by fluoroscopy and x-ray.

2. Eighteen cases, 1.8 per cent, of unsuspected clinically important tuberculosis and 11 additional cases, 1.1 per cent, of clinically unimportant reinfection tuberculosis, a total of 29 cases, or 2.9 per cent, were found by this technique. This incidence was found to be approximately the same as for other nonpregnant women of the same age groups examined at Provident Hospital.

3. These findings are compared with those reported by Eisele and associates[1] at the Chicago Lying-in Hospital, where the incidence of unsuspected clinically important tuberculosis was 1.0 per cent. It is

concluded that the difference is probably due more to the different economic and social status of the two groups than to race, or to a slight difference in their age distributions.

4. The finding of so high an incidence, especially in the Negro in whom tuberculosis tends to run a more unfavorable course, serves to confirm the contention that routine chest roentgenologic examinations should be an indispensable part of the prenatal care of Negro pregnant women.

The patients seen at Provident Hospital were under the supervision of Dr. Pedro M. Santos, Senior Attending Obstetrician. The fluoroscoping was carried out under the direction of Dr. Robert G. Bloch, Professor of Medicine, the University of Chicago. To them, and to others who assisted in the fluoroscopies at various times, the authors wish to extend their thanks and acknowledgment for cooperation received.

References

1. Eisele, C. W., Tucker, W. B., Vines, R. W., and Batty, J. L.: Am. J. Obst. & Gynec. **44**: 183, 1942.
2. Bloch, R. G., Tucker, W. B., and Bryant, J. E.: J. A. M. A. **115**: 1866, 1940.
3. Bloch, R. G., Tucker, W. B., et al.: Report in preparation, to be published.
4. Edwards, Herbert R.: Am. Rev. Tubere. **41**: Supplement, June, 1940.
5. Lewis, Julian H.: The Biology of the Negro, Chicago, University of Chicago Press, 1942, pp. 116-154.

A MINIMUM BACTERIOLOGIC CRITERION OF CURE OF GONORRHEA IN WOMEN*

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THE problem of establishing cure of gonorrhea in the female with a reasonable degree of assurance has always been difficult, both from the clinical and the bacteriologic viewpoint. A further complication to this uncertain problem is the tendency of certain of the sulfonamides to effect clinical subsidence of the infection without elimination of the gonococcus. Reports of a carrier state or latency following sulfonamide therapy, and sulfanilamide especially, have been frequent.[2, 6, 12, 18, 19] Such infections not only constitute a serious public health problem but are also potentially capable of acute and severe exacerbations at a later time.

The general unreliability of the stained smear for the detection of the gonococcus in female infections, and particularly in chronic and latent conditions, is well recognized; so that cultural methods, where available, are more generally relied upon to establish cure and to detect residual infection. Assuming that clinical cure has been established

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following treatment, a second obviously important consideration is the choice of a reliable minimum number of negative cultures to be required before the patient is released as bacteriologically cured. Of significance also is the spacing of such cultures, especially with relation to the menstrual cycle. A review of the literature, however, indicates that the choice of a bacteriologic standard of cure is in most instances haphazard and arbitrary and without any rational basis beyond the experience and convenience of the investigator. For example, the number of negative cultures required for release of the patient following treatment may vary from none at all[5, 17] to as many as 17 or more.[3, 7, 14] In the male, the published criteria of cure are astonishingly varied. To illustrate this point Table I lists the criteria of cure of gonorrhea in the female in some of the more recent literature reports.

TABLE I. CRITERIA OF CURE OF GONORRHEA IN THE FEMALE

INVESTIGATORS	CRITERIA OF CURE			
	SMEARS	CULTURES	POST-TREATMENT OBSERVATION	CLINICAL REQUIREMENTS
Committee on Gonorrhea in the Female (USPHS) June, 1940[1]	12*	12*	4 months	Disappearance of signs and symptoms
Committee on Gonorrhea in the Female (USPHS) June, 1941[1]	6	6	Through 2 menstrual cycles	
Lewis[12] (1940)	8-10	4	4 months	"Clinical cure"
Smith and Deakin[19] (1942)	6*	6*	Through 2 menstrual cycles	"Clinical cure"
Mahoney, et al.[16] (1940)	3 (min.) to 10 or more.	3 (min.) to 10 or more.	Variable	"Remission of clinical evidence of disease"
Moffett[17] (1940)	6-8	None	Through 2 menses	
Jacoby[8] (1941)	12*	12*	5 months	Absence of all clinical signs and symptoms
Mahoney, et al.[14] (1941)	17*	17*	2 months	Absence of signs and symptoms
Fogan (and Newsome) (1939)[4]	3	3	3 months	
Fletcher, et al.[3]	12-36*	12-36*	3-9 months	
Grodberg and Carey[5]	3*	None	1 month	At least 1 pre- or post-menstrual smear
Hesseltine, et al.[7] (1941)	17	17	3 months	Cultures before, during and following menses

*Both urethral and cervical cultures specified.

Recently Mahoney and colleagues[15] have demonstrated the necessity of repeated culture for detection of the gonococcus in chronic infections. Of 367 prostitutes having negative cultures on entrance into a closed institution, 61 (16.6 per cent) yielded subsequent positive cultures, this in spite of the fact that 10 to 20 culture plates were inoculated at each examination.

The problem may be stated as the desirability of determining the minimum number of cultures required during a minimum observation period to detect a maximum of residual infections. Although the studies reported here are preliminary and are concerned only with the bacteriologic aspect of the problem, it is hoped that they will stimulate further attempts to establish a safe standard criterion of cure in both female and male.

Procedure

The patients involved in this study were treated and observed in the out-clinic of the John Sealy Hospital, a procedure which unavoidably introduces an error of considerable magnitude in the following data. The usual routine consisted of:

1. Clinical and bacteriologic diagnosis of gonorrheal infections;
2. Treatment with sulfonamides;
3. Culture and hematologic examination during treatment;
4. Bacteriologic tests at weekly intervals for two to four months after completion of therapy.

Many patients failed to complete the prescribed course of treatment or the follow-up, and a relatively high proportion suffered recurrences, either from relapse or reinfection. On the other hand, many cases have been followed for a year or more.

Each cervical swab was plated directly on one plate of Proteose 3, hemoglobin agar,* which was incubated and examined by the accepted methods. Positive cultures were confirmed by the usual differential tests, particularly if there was reason to doubt the identity of the organism. These results have been reported elsewhere.[11]

In a large number of cases, two or more cultures were obtained from the patient before instituting chemotherapy. In many other instances, a succession of two or more cultures was taken over a period during which the patient was believed to be infected regardless of treatment received. Some of these patients constituted proved sulfonamide-resistant cases; others represented treatment failures because of inadequate or irregular treatment, or for other reasons.

Results

In order to arrange the data for analysis, each patient's record was studied in an effort to determine how many successive cultures were obtained during the period in which the patient exhibited any evidence of infection, either bacteriologic, clinical, or epidemiologic. Those patients having clinical or bacteriologic recurrences following treatment were considered as having been infected continuously, regardless of the number of intervening negative cultures, unless strong evidence of reinfection could be established. Thus, the number of successive cultures taken from infected patients varied from two in many individuals to thirty or more in a few. To illustrate, the culture protocols of 6 patients are presented:

In Case 1, clinical cure followed the three successive positive cultures obtained before sulfapyridine therapy was instituted. In Case 4, reinfection was not proved following the first course of sulfonamides, nor

*A supplement of unautoclaved liver or yeast extract is required to supply a thermolabile nutrilite necessary for growth of a significant proportion of the strains of gonococcus encountered in our studies.[21]

was complete clinical cure obtained; hence six consecutive cultures are counted in this case. Patient 5 became an asymptomatic carrier following an initial irregular course of sulfapyridine and was believed to have harbored the infection continuously during the entire period of observa-

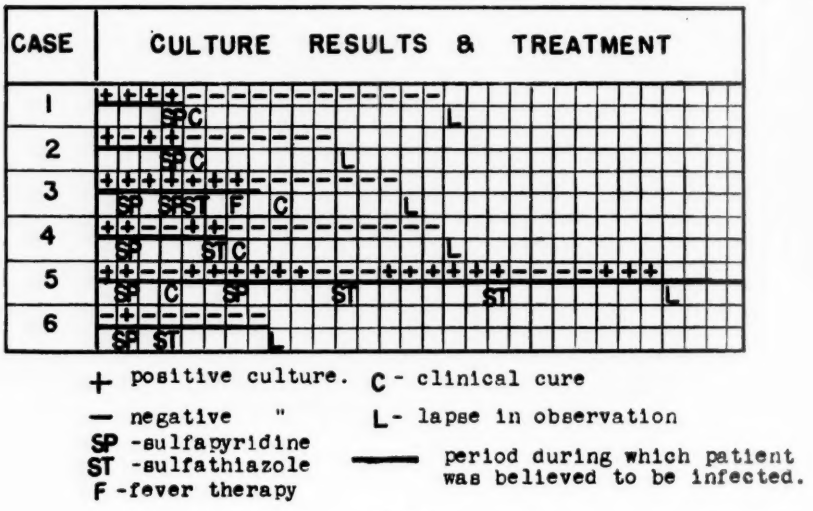

Fig. 1.

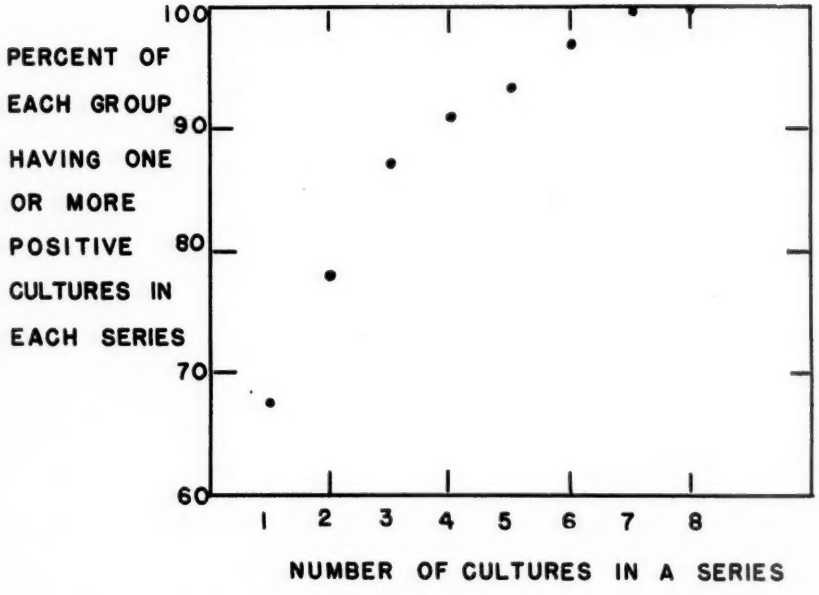

Fig. 2.

tion. Persistent clinical evidence of gonorrhea in Patient 6, despite negative cultures following chemotherapy, necessitate inclusion of all eight cultures in this series.

The culture results of each patient were tabulated in the ascending order of the number of successive cultures obtained during the period

in which the patient was believed to be infected. Each of the longer series (e.g., Patient 5 above) was subdivided into smaller series, having 2, 3, 4, etc., consecutive cultures. In Table II are recorded the number of series in each group having two consecutive cultures per patient, three consecutive cultures, and so on up to the group having eight or more successive cultures per patient. Thus, there were 156 series in the group having four successive cultures; of these, four consecutive cultures yielded *at least one* positive culture in 91 per cent of these cases. On the other hand, of the 54 series of seven consecutive cultures from infected individuals, the gonococcus was detected at least once in every series.

TABLE II. PERCENTAGE OF INFECTIONS DETECTED BY CULTURE

NO. OF CULTURES IN EACH SERIES	NO. OF SERIES IN EACH GROUP	NO. OF SERIES IN EACH GROUP WITH AT LEAST ONE POSITIVE CULTURE	PER CENT OF SERIES IN EACH GROUP WITH AT LEAST ONE POSITIVE CULTURE
1	1270	860	67.7
2	587	481	78
3	262	229	87.4
4	156	142	91
5	95	89	93.7
6	68	66	97.2
7	54	54	100
8 (or more)	36	36	100

By plotting the percentage of each group having one or more positive cultures in each series of consecutive cultures against the number of successive cultures in the series, a curve is suggested. Of the total number of cultures taken (1,270), 860, or 67.7 per cent, were positive; a single culture, therefore, might be expected on this basis to detect 68 of 100 infections. If 2 consecutive cultures are obtained, 78 of 100 would yield one or both cultures positive; with 4 consecutive cultures, from 1 to 4 positive tests might be expected in 91 of 100 cases.

A point is soon reached, however, at which the law of diminishing returns becomes operative, so that the percentage of additional residual infections detected by more than 6 or 7 successive cultures would scarcely be worth the added effort. This is the point which might be adopted as a minimum bacteriologic criterion of cure.

Discussion

In presenting the foregoing data and proposing, for example, that six successive negative cultures be adopted as a reasonably safe minimum for release of treated cases, the authors realize that a formidable array of errors and omissions are involved. To list a few:

1. The impracticability of applying to every individual the results of group analysis.

2. The unreliability of any data obtained in dispensary studies relative to relapse and reinfection.

3. The use of culture data from both treated and untreated cases.

4. The arbitrary method of arranging the data and the decisions to include or exclude certain cultures from a series.

5. The probable inclusion of some cases not infected during a period of the study and exclusion of others who may have harbored residual infection.

6. The proved occurrence of sporadic positive cultures in a long series of negative cultures in some individuals (15).

7. The failure to consider the time element in the follow-up studies.

8. Difference in culture media and bacteriologic technique will influence the yield of positive cultures in various laboratories.

The studies of Mahoney and others,[15] which were conducted in the House of Detention for Women of the Department of Correction of New York City, are subject to far greater control than is possible in clinic studies. Only in some such closed institution, in which the variables are reduced to a minimum, could a study of this type be conducted adequately. The demonstration by these investigators of the occurrence of sporadic positive cultures following a long series of negative tests, and of the permanent reversal of culture positivity in a high percentage of untreated chronic cases, emphasizes the need for great conservatism in the interpretation of results of negative bacteriologic tests, particularly in the presence of any clinical evidence of infection. These results do not, however, nullify the need for, nor the desirability of some *minimum* bacteriologic standard for routine follow-up observation. Nor should the clinician dogmatically assign any residual pathologic signs or symptoms following treatment to a persistent gonorrheal infection in the event of repeated negative cultures. The causes of chronic leucorrhea and pelvic pathology are not only many and varied, but present also an extremely difficult problem of differential diagnosis from chronic gonorrhea, considered from the clinical standpoint alone.

It is recognized that no practical number of cultures will detect *all* residual infections, since, as Mahoney[15] and Lewis[13] have pointed out, the gonococcus may recede to the deep glandular crypts of the cervix, to be discharged at sporadic and infrequent intervals. Therefore, the foregoing results should not be interpreted to mean that 6 to 8 cultures will detect 100 per cent of all infections, but rather a *majority* of residual infections.

Any satisfactory follow-up should extend for a sufficient length of time. It is highly improbable that six cultures taken on successive days following cessation of chemotherapy would be as effective in detecting residual infection as six cultures at weekly intervals, including one or two menstrual cycles. The studies of Fletcher, Gibson, and Sulkin[3] bear out this point. In a series of 194 cases, six weekly cultures following therapy sufficed to detect all probable relapses, although the observation period was extended for thirty-six weeks. Of three recurrences at the fifteenth week, "the possibility of reinfection was established before they were listed as new cases."

Artificial provocation measures, i.e., chemicals and vaccines, have been abandoned largely as tests for cure. The provocative effect of menstruation, however, seems rather well established,[5, 7, 9, 10, 20] and unless a more thorough reinvestigation of the problem should indicate otherwise, it is best included among the tests for cure, with one or two postmenstrual cultures being obtained during the observation period.

Summary

1. Repeated cultures may be necessary to demonstrate the gonococcus in chronic and latent infections, particularly following chemotherapy.

2. Negative smears have no value as a bacteriologic test for cure, and indeed the smear might well be abandoned altogether for this purpose.

3. On the basis of data presented, it would appear that six successive cultures will detect a high percentage of residual gonococcal infections.

4. It is suggested that a *minimum* of six negative cultures at weekly intervals, including one or two postmenstrual cultures, be obtained before a patient is released from observation.

References

1. Committee on Gonorrhea in the Female, June, 1940, and June, 1941. Unpublished.
2. The Executive Committee of the American Neisserian Medical Society: Ven. Dis. Inform. **23**: 88, 1942.
3. Fletcher, P. F., Gibson, O. J., and Sulkin, S. E.: J. A. M. A. **117**: 1769, 1941.
4. Fogan, R., and Newsome, H. P.: Brit. M. J. **2**: 138, 1939.
5. Grodberg, B. C., and Carey, E. L.: New England J. Med. **218**: 1092, 1938.
6. Herrold, R. D., and Palmer, E.: Am. J. Syph., Gonor. & Ven. Dis. **22**: 705, 1938.
7. Hesseltine, H. C., Hac, L. R., Adair, F. L., and Hibbs, D. A.: Am. J. Syph., Gonor. & Ven. Dis. **25**: 454, 1941.
8. Jacoby, A.: J. Michigan Med. Soc. **40**: 435, 1941.
9. John, F.: Arch. f. Dermat. u. Syph. **174**: 96, 1936.
10. John, F.: Dermat. Ztschr. **75**: 65, 1937.
11. Lankford, C. E.: Texas State J. Med. **37**: 553, 1941.
12. Lewis, R. M.: Connecticut M. J. **4**: 662, 1940.
13. Lewis, R. M.: Ven. Dis. Inform. **22**: 352, 1941.
14. Mahoney, J. F., Van Slyke, C. J., and Wolcott, R. R.: Ven. Dis. Inform. **22**: 425, 1941.
15. Mahoney, J. F., Van Slyke, C. J. Wolcott, R. R., Thayer, J. D., and Nimelman, A.: Am. J. Syph., Gonor. & Ven. Dis. **26**: 38, 1942.
16. Mahoney, J. F., Wolcott, R. R., and Van Slyke, C. J.: Am. J. Syph., Gonor. & Ven. Dis. **24**: 613, 1940.
17. Moffett, M.: Brit. M. J. **2**: 8, 1940.
18. Pelouze, P. S.: Am. J. Syph., Gonor. & Ven. Dis. **23**: 48, 1939.
19. Smith, D. R., and Deakin, R.: Am. J. Obst. & Gynec. **43**: 296, 1942.
20. Wendelberger, J., and Dolega, E.: Dermat. Ztschr. **75**: 8, 1937.
21. Lankford, C. E.: J. Bact. **44**: 139, 1942 (abst.).

CALCIUM AND QUININE IN LABOR AND POST-PARTUM HEMORRHAGE

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QUININE has long been employed to stimulate contractions in the pregnant uterus, but has fallen into disrepute somewhat in recent years because of reported ill effects on babies.

Calcium has been credited with various effects upon different organs. It is used for relaxing such organs as the gall bladder and has enjoyed a certain amount of popularity as an antispasmodic in dysmenorrhea. Its effect varies in different animals and often in different concentrations.

The pediatrician and internist are familiar with tetany occurring in children and chronic nephritics where the serum calcium falls below a level of 9 mg. per cent. In ether anesthesia it has been shown that serum calcium drops but not to the level causing tetany. Tetany from over ventilation is probably caused by a relative alkalosis and the resulting relative calcium deficiency.

Body calcium is found fixed in certain tissues and as serum calcium, which consists of two physiologically distinct fractions which have been termed diffusible and nondiffusible. The amount and state of the body calcium is dependent not only upon the amount ingested but also upon certain vitamins, notably vitamins A and D, as well as such hormones as para-thor-mone. The diffusible form of serum calcium will pass through artificially prepared membranes. It ranges in concentration from 4.5 to 5.5 mg. per cent. A small fraction of this diffusible calcium is in the ionized form. In normal pregnancy there is a decrease in serum calcium but rarely below the accepted normal. This alteration is evidenced by progressive decrease in the nondiffusible fraction and a slight increase in the diffusible fraction. Calcium will restore the contractility of smooth muscle that has been temporarily depressed by other ions. The normal serum calcium level is 9 to 11 mg. per cent; however, it becomes toxic only when a level of 23 to 26 mg. per cent is reached.

In Danforth and Ivy's work on the effect of calcium on uterine contractility they showed that an optimum concentration of calcium was necessary to maintain the contractility of the uterus. They also showed that such agents as pituitrin and ergot were not as effective if there was a deficiency of serum calcium.

Mussey studied the effect of calcium gluconate upon 27 pregnant patients and concluded that it was an efficient oxytocic.

Our patients were divided into three series: one group received calcium and quinine in combination, either intramuscularly or intravenously, a second group received calcium gluconate intravenously, while a third group received calcium gluconate intravenously after the third stage, in case of hemorrhage from a relaxed uterus.

The terminology used to describe the effects is as follows: no results means no uterine contraction in response to the medication, fair result means contractions for awhile which subsided without the patient coming to delivery, good result means that existing contractions were either increased or that contractions were initiated and lasted until delivery was accomplished.

The patients in whom we attempted to induce labor varied from seven months' gestation to five weeks overdue. In some the membranes were intact and in others they were ruptured.

Analysis of Results

Thirty-five patients received calgluquine,* a preparation consisting of calcium gluconogalactogluconate 0.1375 Gm. and quinine gluconate 0.06 gr. (0.037 Gm. of anhydrous quinine base) per c.c. There were 18 primigravidas and the rest multiparas. The average number of pregnancies for the group was 1.71 per patient. The average age of the group was twenty-seven years. In 13 patients the membranes were ruptured, and intact in 22. Twenty-four had no dilatation of the cervix, while 11 had varying degrees of dilatation. There was 1 breech presentation, the rest were cephalics.

The average initial dose was 4 c.c. and the average total dose per patient was 8 c.c. Four patients received the medication intravenously while the rest received it intramuscularly.

There was good response in 20 patients. Ten of these were from the 13 who had ruptured membranes. Only 10 of the 22 with intact membranes gave satisfactory response.

In 7 patients, who were from seven to eight months' gestation, 3 were not in labor but early delivery was desired for medical reasons. None of them went into labor after the calgluquine. In four patients of seven to eight months' gestation, 2 were having irregular pains and 2 were not in labor. All of them went into satisfactory labor shortly after the medication, and delivered.

There were 4 mild toxemias. Among the term patients only one responded to calgluquine, and she was well advanced in labor when it was given. Two of them had previously been given magnesium sulfate parenterally. Whether there was an antagonistic action, thus preventing the onset of labor, we do not know.

The 35 labors terminated as follows: 22 spontaneous deliveries, 9 forceps deliveries, 2 cesarean sections, 1 version and extraction, and 1 breech extraction. Of the forceps deliveries, only 3 were necessary, the remainder were for teaching purposes.

Two Bandl's rings were found. Both were in patients who had long labors and "stalled" because of cephalopelvic disproportion. One was terminated by version and extraction and the other by cesarean section. Neither of these patients should have been given a uterine stimulant.

*Calgluquine is a product of the Sandoz Chemical Works, Inc., New York, N. Y.

There were 2 dead babies. One was in the case of the patient who had a large baby with cephalopelvic disproportion and Bandl's ring. In the other the mother had a severe fall preceding delivery, and no fetal heartbeat tones were heard shortly thereafter.

There were 2 asphyxiated babies. One was a premature infant who had a precipitate labor and the other had a difficult forceps delivery.

There were no ill effects that could be attributed to the quinine.

Calcium Gluconate

Calcium gluconate alone was given to 12 patients to stimulate labor pains. Six were primiparas and 6, multiparas. The average number of pregnancies was 1.83. The average age was 24.16 years. Nine of them were at term, one two weeks overdue, one seven months, and one three months' missed abortion.

The term patients all had cephalic presentations. Ten had no cervical dilatation, while 2 had 3 cm. to 4 cm. dilatation. The membranes were ruptured in 4 and intact in 8. Three of those with intact membranes responded to calcium gluconate, and 2 others had some pains which faded out. The three months' missed abortion had no effect from the medication.

The initial dose was 4 c.c. to 5 c.c. intravenously. The average total dose was 8 c.c. of the 10 per cent calcium gluconate solution.

Two patients had precipitate labors following the medication. There was one asphyxiated seven months' baby. There was one dead baby, the death of which was apparently caused by a prolapsed cord.

These 12 pregnancies were terminated as follows: 10 delivered spontaneously, one was delivered by version and extraction, and one by forceps.

There was one Bandl's ring in an overweight colored primigravida who had a large fetus. The fetus was delivered by version and extraction with difficulty after adrenalin was given and she was under deep anesthesia.

The one forceps delivery was occasioned by cephalopelvic disproportion.

Calcium Gluconate in Hemorrhage

Calcium was used fourteen times in 4,000 deliveries to check hemorrhage in atonic uteri.

In the post-partum patients who received calcium for hemorrhage, the customary post-partum medication, usually pitocin and ergot, had, as a rule, been given at the end of the third stage with little or no effect. Some of them had been given a second dose of ergotrate intravenously. In addition to the medication, massage had been used in most instances without result. No attempt was made to stop hemorrhages from uteri with lacerated cervices or from vaginal lacerations by the use of calcium gluconate. It was given intravenously and usually in doses of 5 c.c. Three patients received 10 c.c. but the results were apparently no different.

In this group of patients the hemorrhage occurred in some immediately after delivery and in others as late as nine hours after delivery; still others had immediate post-partum hemorrhage and bled again some time after returning to the ward.

There were 7 primiparas and 7 multiparas. The high incidence of primiparas is probably explained by the larger number of operative

deliveries in this group. Their average ages were 21.33 years and was irrelevant.

Seven delivered spontaneously, 6 had forceps deliveries, and 1 was a breech extraction. Of the spontaneous deliveries, 1 had a four months' abortion and retained the placenta. She bled when the placenta began separating.

The weights of the babies from the women at or near term varied from 2 pounds 7 ounces to 10 pounds 4 ounces. There were no twins or polyhydramnics.

The length of the labor was irrelevant. In some it had lasted over a couple of days while in others it had been very rapid.

There was one lacerated cervix which was repaired after manual removal of the placenta. The uterus failed to contract well.

Six patients had surgical ether, 1 surgical chloroform, 3 obstetric chloroform, 1 cyclopropane, 1 local anesthesia, and 1 nothing at all.

The higher incidence of hemorrhage occurring after ether might be explained by the fact that it was the most commonly used anesthetic for operative obstetric procedures. All of the ether anesthetics were terminated by operative means. One of the chloroform patients and the patient with local anesthesia had operative deliveries. The remainder were spontaneous.

The effect of the calcium gluconate is hard to determine in some few cases; however, in the majority, it was clear-cut. The patient who had an incomplete abortion and retained placental tissue did not respond at all. She is the only one that required packing.

The usual routine was to give pitocin, ½ c.c., at the end of the second state and ergotrate, $\frac{1}{320}$, at the end of the third stage intramuscularly.

In 8 patients there was an immediate post-partum hemorrhage following the third stage, which did not stop after ergotrate. Four received an additional dose intravenously, with partial or no response. The uterus remained baggy and there was a continual stream of blood which varied from a trickle to a gush. Calcium gluconate usually, in 5 c.c. doses, brought about a marked hardening of the uterus with a prompt decrease in bleeding in 7 of the 8 patients.

In the remaining patients the hemorrhage started from twenty minutes to nine hours after delivery. They usually left the delivery room in good condition. Two had some excess bleeding at the time of delivery. When the bleeding was discovered on the ward, they were given intramuscular ergotrate, $\frac{1}{320}$, which was followed by intravenous calcium gluconate, 5 c.c., in fifteen minutes to thirty minutes if bleeding continued. Four of the 6 had prompt diminution of the flow. However, the exact effects are hard to evaluate as the ergotrate may have been slow to act in some cases. The bleeding in some would probably have checked had we been able to wait. But in others the effect of the calcium was dramatic. Five of this delayed group of bleeders had been given surgical ether for operative deliveries.

Summary

1. The combination of calcium and quinine was apparently a little more effective than calcium gluconate alone.

2. The intravenous route of administration alone was used in the patients receiving calcium gluconate, and in 6 of the patients receiving

calgluquine. The response was more prompt than the intramuscular route, in that some of these had precipitate labors.

3. The best results were obtained where the patients had ruptured membranes or were already having mild pains.

4. No ill effects on the babies from the quinine were noted in this series; however, the dose was small.

5. Three Bandl's rings were found. All had more or less cephalopelvic disproportion which was probably the principal factor in the Bandl ring.

6. Patients with post-partum hemorrhage from atonic uteri that had not responded to the usual oxytocics had, as a rule, a marked hardening of the uterus and a lessening of the hemorrhage immediately after receiving intravenous calcium gluconate.

Discussion and Conclusions

Calcium salts alone or in combination with small amounts of quinine are useful in initiating contractions in patients with ruptured membranes. They are also valuable in patients with "piddling" labors. Care should be exercised that a cephalopelvic disproportion is not present as these drugs are contraindicated here. One should be careful to distinguish between a "stalled" labor from dystocia and one of the "piddling" type that has ineffectual pains. If quinine is to be used, the history of drug dyscrasias should be learned.

Calcium is to be avoided, or at least used very carefully, in patients on digitalis or related drugs.

The most gratifying results were obtained in the management of post-partum hemorrhage. In some cases dramatic results were obtained. In other cases the uterus had partially contracted but bleeding continued with a trickle until calcium was given, then the uterus contracted tightly. The one case of incomplete abortion was not benefited.

References

1. Ivy, A. C.: Northwest Med. **39**: 16, 1940.
2. Danforth, W. C., and Ivy, A. C.: Am. J. Obst. & Gynec. **37**: 194, 1939.
3. Patton, G. D., and Mussey, R. O.: Am. J. Obst. & Gynec. **41**: 948, 1941.

CLINICAL EVALUATION OF TESTOSTERONE PROPIONATE AND METHYL TESTOSTERONE IN DYSMENORRHEA AND MENOMETRORRHAGIA

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PAINFUL menstruation and functional uterine bleeding have always presented major therapeutic problems in gynecology. Male hormone preparations have been used in the treatment of these disorders by a great number of investigators with varying success. This report is concerned with the effects and results obtained by the administration of testosterone propionate* and methyl testosterone* in a series of 20 cases of dysmenorrhea and a series of 15 cases of menorrhagia or menometrorrhagia.

Dysmenorrhea

No effort was made to select these cases. Patients were taken consecutively just as they appeared in the clinic. The treatment was planned to consist of a 10 mg. injection of testosterone propionate administered intragluteally every other day, starting two weeks before the expected onset of menstruation. The therapy was followed so far as possible. However, since it necessitated visits to the clinic on the part of the patients, there was some irregularity, i.e., deviation from the original plan. In appraising the results, two cases of the original series of 20 were omitted because of inadequate therapy due to lack of cooperation and incomplete observation. Of the remaining 18 patients, 4 experienced complete relief during the period of observation, 8 experienced partial relief, the reduction of pain varying from 25 to 75 per cent; 6 experienced no improvement. The period of observation extended from two to seven months. Of the 12 patients who were relieved, pain recurred in 7 upon discontinuation of medication. The following case histories are given as typical instances:

CASE 1.—M. M., aged 32 years. *Chief complaint:* Painful menstruation. *Diagnosis:* dysmenorrhea, cervicitis, third-degree retroversion. Prior to the menstrual period in February, 1941, the patient was given eight injections of testosterone propionate, 10 mg. each, and the period in February was painless. No treatment was given during the next two menstrual cycles, and the menstrual flow at the end of each cycle was painless. For three days before the onset of menstruation in May, the patient had severe pain which was not relieved by sedatives.

*Testosterone propionate (Neo-Hombreol) and methyl testosterone (Neo-Hombreol [M] Tablets) were supplied by Roche-Organon, Inc., Nutley, New Jersey.

CASE 2.—M. R., aged 32 years. *Chief complaint:* painful menstruation. *Diagnosis:* dysmenorrhea, cervicitis, parametritis. Prior to the menstrual period in February, 1941, the patient received six injections of testosterone propionate, 10 mg. each, and the flow was slightly less painful. Before the period in March, due to external circumstances, she received only three injections (30 mg. of testosterone propionate). Menstruation in March was four days early and was again severely painful. Before the next period, ten injections (100 mg. of testosterone propionate) were given which, however, afforded no relief. Treatment was therefore discontinued.

CASE 3.—S. W., aged 24 years. *Chief complaint:* severe pain during the first two days of each menstrual period. Prior to the period in July, 1940, the patient received four injections (40 mg. of testosterone propionate) and pain during the menstrual period was slightly less severe. Two injections (20 mg. of testosterone propionate) were given before the next menstrual period with subsequent reduction in pain of approximately 50 per cent. Three injections (30 mg. of testosterone propionate) were given before the September menstrual period, but they did not, however, result in improvement. Although no hormone therapy was given prior to menstruation in October, this flow was entirely painless. During the following cycle, prior to menstruation, patient received four injections (40 mg. of testosterone propionate) with the result that pain during the menstrual flow was again diminished by about one-half. During the next two cycles treatment was omitted, but improvement continued. The patient was not seen again until November, 1941, at which time she was in the fifth month of pregnancy.

In some of the dysmenorrhea cases, efficacy of methyl testosterone, given by mouth, was evaluated. The dosage schedule was one 10-mg. tablet t.i.d. An attempt was made to determine the ratio of effectiveness between testosterone propionate parenterally and methyl testosterone orally. The following case report will illustrate the method followed in such a determination.

CASE 4.—E. K., aged 26 years. *Diagnosis:* severe dysmenorrhea. Prior to the menstrual period in February, 1941, the patient received eight injections of testosterone propionate, 10 mg. each. Pain during the ensuing menstrual flow was diminished by approximately 75 per cent. No medication was given during the following menstrual cycle, and the flow was just as painful as it was before institution of male hormone therapy. This patient was then given methyl testosterone orally. A total of 63 tablets, 10 mg. each, was ingested during the April cycle, 48 of which were taken during the second half of the cycle. Menstrual pain was reduced by approximately 50 per cent. During the next cycle, 76 tablets were ingested with 75 per cent improvement. Here again, 48 tablets, i.e., 480 mg. of methyl testosterone, were taken during the second half of the cycle. It will be noted that this compares with the dosage of 80 mg. of testosterone propionate administered parenterally. Improvement was maintained during menstruation in June and July without any medication during the cycles. Menstruation in August was again characterized by severe pain necessitating bed rest and hypnotics.

Menorrhagia and Menometrorrhagia

The treatment in this series of cases was planned to consist of 25 mg. injections of testosterone propionate administered intragluteally every other day, starting at least two weeks prior to the expected onset of menstrual flow. However, this plan could not be followed in some cases. If patients presented themselves during the period of excessive bleeding, whether at or between periods, the flow abated promptly after institution of treatment. A single 25 mg. injection frequently was followed by a lessening of the flow. Six patients of the original group of 15 could not be followed for longer than one month and, therefore, are not considered in the final appraisal. Of 9 patients remaining, 6 experienced complete relief from excessive bleeding, 2 were partly relieved, and 1 showed no change. The patients were observed two to nine months after institution of therapy.

The following case histories are illustrative:

CASE 5.—M. A., aged 33 years. *Chief complaint:* Profuse bleeding over a period of seven days. In May, 1941, prior to the menstrual period, the patient received four injections (100 mg. of testosterone propionate). The subsequent period lasted four days and the flow was markedly decreased. No treatment was given during the June cycle and the ensuing menstrual flow was again excessive over a period of seven days. No therapy was employed during the next menstrual cycle either, and here, too, the flow was profuse and lasted eight days.

CASE 6.—E. B., aged 29 years. *Chief complaint:* Excessive menstrual flow, uterine bleeding between periods. Four injections (100 mg. of testosterone propionate) were given to this patient prior to the menstrual period in July, 1941, which lasted four days and was moderate. Also, there was absence of metrorrhagia. No treatment was given during the next cycle, but nevertheless the following menstrual period lasted only four days and was moderate. The same was true of still the next period, although no medication had been employed. Menstruation during October, November, and December likewise was not preceded by any medication and in each instance was slightly more profuse but considerably improved compared with the status before institution of therapy.

Symptoms of masculinization were noted in two patients. There was very slight hirsutism on the face which disappeared shortly after discontinuation of medication. One patient complained of nausea and vomiting following an injection.

Discussion

Since dysmenorrhea is the manifestation of various pathologic conditions, it cannot be anticipated that male hormone therapy will alleviate painful menstruation in every case. Various theories have been advanced as to the cause of functional dysmenorrhea. It seems likely that a disturbance in the normal uterine contractility during menstruation may be the underlying factor of this disorder. Evidence has been presented that male hormone in large doses suppresses uterine contractions.

Alleviation of painful menstruation by administration of male hormone in smaller doses therefore could be on the basis of reducing excessive contractions of the uterus.[1, 2]

The hypothesis that menometrorrhagia may be due to excessive or unbalanced elaboration of estrogen is workable and rational in the light of present knowledge. On the basis of this hypothesis, the beneficial action of the male hormone in excessive uterine bleeding has been attributed to several effects, including suppression of estrogen production and inhibition of the anterior pituitary. However, in this dyscrasia as in dysmenorrhea, the inhibiting action of the androgens on rhythmic uterine contractility may be the reason for their value. In menometrorrhagia, the inhibition of uterine contractility has been shown to decrease the volume of blood flow to the uterus, hence the beneficial results. Furthermore, the androgens have a direct effect on the myometrium, bringing about constriction of the myometrial vessels, thus reducing the volume of blood flow.[3, 4]

The recurrence of symptoms after cessation of therapy would seem to indicate that no permanent alteration in the hormonal balance of the patient had been effected by the therapy of the duration in this study.

Summary

Eighteen patients with dysmenorrhea and 9 patients with menorrhagia and menometrorrhagia were treated with testosterone propionate and methyl testosterone. Complete relief of symptoms was experienced by 4 and improvement by 8 of the dysmenorrhea patients and complete relief by 6 and improvement by 2 of the menometrorrhagia patients. Thus, androgen therapy was completely or partially effective in 67 per cent of the dysmenorrhea cases and in 88 per cent of the menometrorrhagia cases. Practically, in all instances there was a recurrence of the original ailment after discontinuation of treatment at varying intervals. Oral androgenic therapy, if administered in adequate dosage, yields the same result as parenteral therapy.

References

1. Salmon, U. J.: J. Clin. Endocrin. **1**: 162, 1941.
2. Greenhill, J. P., and Freed, S. C.: Am. J. Obst. & Gynec. **39**: 636, 1940.
3. Sturgis, W. C., Abarbanel, A. R., and Nader, D. S.: Am. J. Obst. & Gynec. **39**: 102, 1940.
4. Abarbanel, A. R.: Am. J. Obst. & Gynec. **39**: 243, 1940.

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THE NORMAL AMOUNT OF CEREBROSPINAL FLUID PRESENT WITHIN THE SKULL AT BIRTH

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THE amount of cerebrospinal fluid which can be demonstrated within the skull of a fetus or a newborn infant at necropsy varies normally in relation to the gestational age. An increase in fluid is occasionally observed which is independent of age and which, in some instances, seems to be related to the method of delivery.

We have been unable to find information concerning the actual amount of fluid present in the extracerebral spaces of the skull under either normal or pathologic conditions during fetal and early infant life. Scammon[1] states that the brain at birth fills the skull more completely than it does at any other time of life; then it occupies 97.5 per cent of the cranial cavity in contrast to 92.5 per cent in the adult. We have observed at necropsy that there is no visible fluid in the meninges of the majority of infants at term, and believe that the close approximation of the brain to the skull which is normally present occasionally causes an erroneous diagnosis of edema of the brain.

It is known that only a very little fluid can be obtained by spinal puncture within the first few days of life. However, the amount obtained from the spinal canal is not necessarily proportionate to the amount present within the skull. Levinson[2] found that from a few drops to 5 c.c. with an average of 3 c.c. could be obtained by spinal puncture on the first day of life, and that from 1.5 c.c. to 10 c.c. with an average of 6 c.c. could be obtained by cisternal puncture.

In order to measure the amount of fluid present within the skull at post-mortem examination we have devised a method which, although not entirely accurate, permits determination of the approximate amount of fluid and enables one to make comparisons of the amounts present in the heads of different infants.

Procedure

The scalp is reflected and the head is opened by cutting a large circular disc from each parietal bone in such a way that the dural sinuses remain intact. An inspection of the surface of the brain, and a general evaluation of the amount of blood and fluid within the head can then be easily made, a procedure which is much more difficult if vessels are incised in opening the skull.

While the skull is being opened, and the brain and supporting structures examined, the head is held over a pan so that the fluid which escapes is not lost. The brain after inspection in situ is removed into the same pan and any fluid remaining in the cranial vault is added. Two layers of fine meshed surgical gauze are immersed in water, wrung as dry as possible, and placed over the top of a wide-mouthed jar. The brain and all of the material within the pan are emptied into the cloth and the fluid is permitted to filter through. At the end of fifteen minutes the fluid is measured.

It is impossible to remove the brain without loss of blood from the cerebral vessels and dural sinuses. In order to estimate the proportionate amount of blood in the total fluid the cell volume of a representative sample is determined by use of a Wintrobe hematocrit tube.

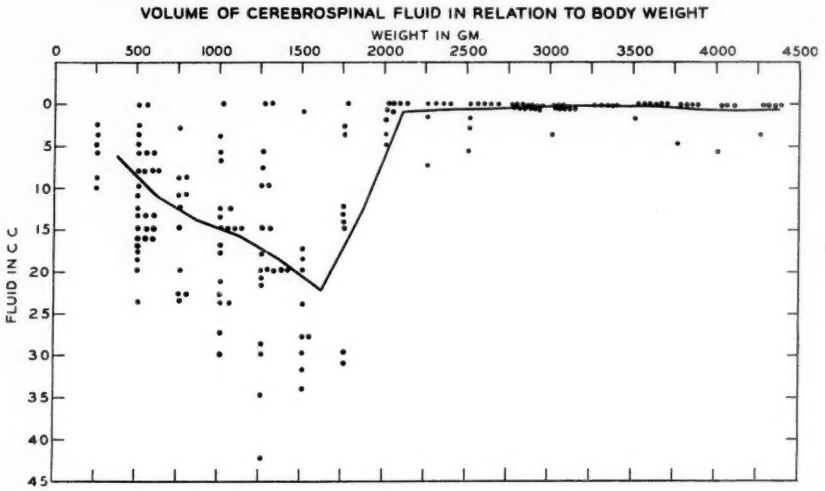

Fig. 1.

The cell volume is considered to represent one-half of the total blood volume, and the hematocrit reading is doubled to obtain the percentage of blood in the specimen. Minute particles of brain tissue often pass through the gauze and form a separate layer above the blood cells in the hematocrit tube. The amount of brain tissue may also be calculated from the percentage noted in the hematocrit tube. This, too, must be subtracted from the total volume. If, therefore, 15 c.c. of blood-tinged fluid is obtained, and the hematocrit reading is 4 per cent red blood cells and 2 per cent brain substance, the blood and brain tissue will amount to 10 per cent of the total measured volume. The corrected volume is consequently 13.5 c.c.

Results

The volume of intracranial fluid has been measured in 225 infants and fetuses. From this series we have eliminated all macerated fetuses, all infants living more than twenty-four hours, and all who died of intracranial hemorrhage, fetal hydrops, hydrocephalus, and other malformations in which excessive fluid may be found. In tabulating the various fluid volumes, it was noted that delivery by cesarean section is unusually frequent among the infants in whom the larger volumes are

found. It was also observed that these infants and those who were delivered immediately after artificial rupture of the membranes made up the majority demonstrating the higher fluid volumes. The possibility therefore arises that delivery by these methods may be accompanied by an abnormal accumulation of fluid. (These infants are being studied separately and are to be reported at a later date.) In order to obtain a curve showing normal volumes of fluid, it was deemed advisable to eliminate all of those delivered by cesarean section, or immediately after artificial rupture of membranes. The resulting curve is similar to the one in which all cases are included, except that it follows a slightly lower course.

It would seem that these figures, then, may be considered representative of the normal amount of fluid present within the cranial vault in infants of varying birth weights. They are based on the findings in 170 selected infants and fetuses. The averages in relation to body weight are shown in Table I, and the range in relation to body weight in Fig. 1.

TABLE I. AVERAGE AMOUNT OF CEREBROSPINAL FLUID IN RELATION TO BODY WEIGHT

BODY WEIGHT GM.	VOLUME OF CEREBROSPINAL FLUID C.C.
250- 499	6.5
500- 749	11.4
750- 999	14.6
1,000-1,249	15.8
1,250-1,499	19.6
1,500-1,749	23.3
1,750-1,999	13.6
2,000-2,249	1.6
2,250-2,499	1.3
2,500-2,749	1.3
2,750-2,999	0
3,000-3,249	0.5
3,250-3,499	0
3,500-3,749	0
3,750-4,000	1.0

Conclusions

The amount of cerebrospinal fluid found within the cranial cavity at the post-mortem examination of 170 selected infants and fetuses is reported. The amount increases gradually from 7 c.c. in the weight group of 250 to 500 Gm., to 23 c.c. in the weight group of 1,500 to 1,750 Gm. Thereafter it falls abruptly, and in all infants and fetuses weighing over 2,000 Gm., practically no fluid can normally be demonstrated by the method used.

References

1. Scammon, R. E.: Abt's Pediatrics 1: 318, Philadelphia, 1925, W. B. Saunders Co.
2. Levinson, A.: Am. J. Dis. Child. 36: 799, 1928.

OVARIAN AUTOGRAFTS

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OVARIAN autografting has been done in an attempt to supply ovarian secretion to those patients in whom surgical removal of both ovaries was necessary because of some nonmalignant ovarian disease. According to most authors the original technique for autogenous ovarian grafts was published in 1910 by Tuffier. Many reports favorable to this and modified techniques followed, although recently very little has been written about this procedure probably due in part to the advent of improved estrogenic therapy.

This survey shows that in many respects the results obtained have been good; however, it must be stated that the effects desired have not been completely achieved.

Material and Technique

This is a report of 38 cases of ovarian autografting. These cases have been taken from the record files of the Elizabeth Steel Magee and St. Francis Hospitals in Pittsburgh. This procedure was found to have been performed 38 times in twenty-five years, an average of 1.5 such operations per year in both hospitals. This rather small incidence is due largely to conservative ovarian surgery, although at times bilateral oophorectomy has been done when no ovarian tissue could be salvaged for grafting.

It is interesting that 23 of the 38, or 60 per cent, of the patients had previous pelvic surgery. In 9 of these patients one ovary had been removed. The ovarian pathology of these 23 cases was one of cystic change, the ovaries showing multiple small and large simple or follicular type cysts. Six of the other patients in this series showed pelvic inflammatory disease with peri-oophoritis and multiple follicular cysts of the ovaries. There were three patients with bilateral cystadenomas of the ovaries, two with large corpus luteum cysts of both ovaries, and one with bilateral dermoid tumors. Three patients with endometriosis were subject to ovarian autografting. The value of this procedure for cases of endometriosis subject to bilateral-oophorectomy has been stressed by Counseller, although our records show that conservatism has been the rule for endometriosis, and whenever feasible, one ovary or a remnant of ovary has been left with some intact blood supply.

The age of the patients in this group varied from twenty-one to forty-three, the average age being thirty.

In this series, the earliest cases of ovarian autografting were done by Dr. R. R. Huggins in 1916. The technique then employed was similar to that of Tuffier. Large pieces of normal ovarian substance were implanted in the subcutaneous fat near the laparotomy incision. It was later learned that only the peripheral zones of these grafts survived, and that the central portions underwent necrosis. In eight of these cases the ovarian tissue was grafted into fat.

From 1926 until the present time a modified technique has been used in which multiple thin grafts have been imbedded in one or both recti muscles. The greater available blood supply of the rectus muscle seemed to offer the grafts better opportunity for survival and function. Thin grafts were employed to avoid necrosis. The grafts were small slivers of ovarian tissue measuring from 5 to 10 mm. in length and from 1 to 2 mm. in thickness. They were all cut by scalpel from the cortex of normal appearing ovarian substance, because the greater number of remaining primordial ova are found in a small zone beneath the germinal epithelium. Other authors have strongly advised taking small grafts from the medulla or central portion of the ovary. There were no reasons given, however, for this modification. The ovaries after removal were always kept in a warm saline bath until the peritoneum was closed. The grafts were then cut and placed in small pockets within the rectus muscle which were made by sharply inserting a straight hemostat and spreading it to separate the fibers of the muscle. Each pocket was ample to bury completely one of the grafts, and from eight to sixteen grafts were implanted in each patient. There was at times a small amount of bleeding from the muscle which gradually subsided, and closure of the incision was completed with very little delay. In all cases, the incisions healed by first intention.

Analysis of Results

Adequate follow-up records were available in 26 of the 38 cases reported. Of these, 14 were patients in whom a supravaginal hysterectomy had been done. In the other 12 the uterus had been left in situ. Eleven of the twelve patients not subjected to hysterectomy were given thin ovarian grafts in one or both recti muscles, and all of these patients menstruated. Only one of this group received ovarian grafts into subcutaneous fat. In this patient cystic structures formed at the site of the grafts and excision of these transplants was eventually necessary. This patient never menstruated.

There was considerable variation in the character of the flow and the duration of the menstrual activity of each of the eleven patients treated by placing multiple thin ovarian grafts in the recti muscles. Some of the patients did not have a menstrual flow for two or three months following operation. This latent period has been discussed in other reports and seems to indicate the period of time required for the grafts to establish blood supply and functional activity.

There was some variation in the length of the menstrual cycles, although seven patients menstruated at monthly intervals. Occasionally one of these patients would report a missed period. The cycles of the other four patients showed more variation. One patient menstruated every three months, another every two to eleven weeks, and another menstruated twice in three months and no further report of her cycle was obtained. One other patient menstruated, but the interval between periods was never recorded.

The duration of the flow was recorded for six patients and usually lasted three days. There were two patients who had two-day periods.

The menstrual history of one patient is interesting. Before operation she had prolonged and excessive menstrual flow. Because of pelvic inflammatory disease bilateral salpingo-oophorectomy was necessary. Ovarian autografting was done. Following operation the patient did

not menstruate for two months. Thereafter she menstruated every month for three months, the flow lasting three days. Excessive bleeding recurred. Basal metabolic rates were found to be –16 per cent and –18 per cent. Five grains of thyroid substance were given daily, and the patient has menstruated normally three times in five months.

The duration of the menstrual activity in all the cases showed great variation. The number of years that these patients menstruated may be taken as an indication of the probable length of the life of the grafts. Three patients menstruated for five, seven, and eight years, respectively. There were two patients who menstruated for four years. One patient menstruated for two years, and another menstruated for one year. The period of follow-up for the others was brief and incomplete. The most significant finding of this survey has been that all the patients given multiple thin ovarian grafts into the rectus muscle were able to menstruate, and this seems to be the best evidence of the efficacy of the procedure.

Ovarian autografting has also been done in the hope of reducing the occurrence and the intensity of hot flushes. Twelve patients, or 46 per cent, of the 26 followed postoperatively had no hot flushes. Five patients in this group had hot flushes for two or three months until the grafts were able to establish function. In addition to these patients five others had mild hot flushes which were not disturbing enough to require therapy. This comprised a group of seventeen, or 65 per cent, which showed favorable relief from vasomotor waves. Four of these patients were observed over a period of several months, but the remaining thirteen were seen over a period of years. Nine of the 26, or 35 per cent, had severe hot flushes or hot flushes disturbing enough to require estrogenic therapy.

A greater number of the patients who had been subjected to hysterectomy reported severe hot flushes, and in addition this group showed a greater number receiving estrogenic therapy. Urinary estrogen assays were obtained in seven cases of this series. In all of these patients ovarian autografts had been placed in the rectus muscle. Considerable difficulty was encountered in having patients submit twenty-four-hour specimens of urine to the laboratory. The readings obtained on two patients in whom the uterus had been removed were 4 rat units (or less) per twenty-four hours in one patient; and 6 rat units (or less) per twenty-four hours in the second patient. The readings obtained on five patients in whom the uterus had not been removed were 6 rat units, 10 rat units, 15 rat units, 20 rat units, and 15 rat units per twenty-four hours, respectively. It is apparent that the patients not subjected to hysterectomy tend to have higher urinary estrogen levels.

It is well known that ovarian grafts, regardless of the site of implantation, tend to form cystic swellings. These structures are often painful, particularly those placed in the rectus muscle where there is the factor of greater mobility. Fifteen of the 26, or 57 per cent, of the patients who were followed postoperatively had no discomfort, no swelling, and no tenderness at the site of the ovarian implants. Five of the patients complained of swelling and tenderness at the site of the grafts at monthly intervals. Of the five, three did not have a hysterectomy, and the pain and swelling were reported to occur just before or during menstruation. Two patients subjected to hysterectomy complained of periodic slight swelling and tenderness, and two other cases noted tenderness and swelling which was not periodic.

Four patients, or 11 per cent, had such pain and tenderness with the ovarian grafts that some type of interference was necessary. The operative record in each of these four cases did not indicate the size of grafts employed. It is possible that these grafts were larger and thicker than the thin ovarian grafts described in the technique above. In one of these cases the ovarian grafts had been placed in the subcutaneous fat. This woman never menstruated and she complained of severe hot flushes indicating very little functional activity. Following excision of the grafts her pain and tenderness disappeared.

In the three other patients multiple ovarian grafts had been placed in the rectus muscle. Because of the discomfort one patient was given deep x-ray therapy over the grafts and amenorrhea followed. Two patients were operated upon because of pain and swelling at the site of the grafts. In one case cystic ovarian tissue was excised twice during a two-year period following ovarian autografting. This patient continued to menstruate for three years and had no further discomfort. In the fourth patient regular menstrual flow continued for six years after removal of a cystic graft which had formed one year after implantation. In each case excision of these grafts was very difficult because of marked scarring and profuse bleeding. In the fourth patient cystic swellings reappeared twice at three-year intervals, and complete relief was obtained by aspirating the cysts with a 19 gauge needle. These cysts did not recur, and the functional activity of the grafts apparently was not disturbed. This type of treatment seemed preferable to surgical excision.

The ovarian transplants excised from two patients were examined microscopically. One transplant had been excised one year after implantation and showed activity because of the presence of an active corpus luteum. The ovarian graft in the second patient was excised two years after implantation and here again evidence of activity was shown by the presence of a regressing corpus luteum in a loose ovarian stroma. These corpora lutea were found in addition to larger cystic structures resembling follicular cysts.

There seems to be ample evidence to show that ovarian autografts can establish blood supply and develop some degree of function. The amount of ovarian secretion so supplied is probably small, yet every patient in this series with an intact uterus continued to menstruate following implantation of thin ovarian grafts in the rectus muscle.

This procedure can never be accepted as a substitute for any form of conservative ovarian surgery. It does offer definite benefit to those patients in whom bilateral oophorectomy cannot be avoided. Menstruation continues, menopause is often delayed for years, and the approach to menopause is more gradual in contrast to the abruptness of surgical menopause.

In the final analysis, the choice between ovarian autografts and estrogenic therapy is a matter of judgment for the individual surgeon.

Summary and Conclusions

1. Thirty-eight cases of autogenous ovarian grafts have been analyzed.

2. Ovarian autografts in fatty tissue are not successful.

3. Multiple (from 8 to 16) thin-sliced grafts from ovarian cortex into rectus muscle are recommended. These grafts functioned when

transplanted into rectus muscle as evidenced by menstrual activity usually for years, in 100 per cent of cases with an intact uterus, and by microscopic demonstration of corpora lutea in grafts excised one and two years after implantation.

4. Sixty-five per cent of the 26 patients who were followed showed relief from hot flushes and did not require estrogenic therapy.

5. Painful ovarian grafts are usually due to the development of cysts, excision of which is difficult. Aspiration of the cysts is preferable.

I am deeply grateful to Dr. B. Z. Cashman for the greater part of the clinical material used in this report.

References

1. Counseller, V. S., and Work, D. H.: Surg., Gynec. & Obst. **10**: 220, 1940.
2. Norris, C. C., and Behney, C. L.: Surg., Gynec. & Obst. **49**: 642, 1929.
3. Estes, W. L., Jr.: Surg., Gynec. & Obst. **38**: 394, 1924.
4. Bainbridge, W. S.: Am. J. Obst. & Gynec. **5**: 379, 1923; Am. J. Obst. & Gynec. **5**: 493, 1923.
5. Chalfant, S. A.: Surg., Gynec. & Obst. **21**: 579, 1915.
6. Martin, F. H.: Surg., Gynec. & Obst. **35**: 573, 1922.
7. Tuffier, S. A.: Surg., Gynec. & Obst. **20**: 30, 1915.
8. Estes, W. L., Jr., and Heitmeyer, P. J.: Am. J. Surg. **24**: 563, 1934.

Magee Hospital

DILATATION OF THE URETHRA FOR IRRITABLE VESICAL NECK

J. Craig Potter, M.D., Rochester, N. Y.

THE various symptoms grouped under the heading "irritable vesical neck" are common complaints in gynecologic practice. The object of this paper is to record the results obtained in 100 consecutive cases of this condition treated by dilatation of the urethra.

There is no counterpart to the irritable vesical neck in male urology. It is a symptom complex rather than a clinical entity, for there are few objective findings. The urine is clear; there is no pyuria; the pathologic findings are inconstant and rare.

The four major symptoms are urinary frequency, urgency, burning, and a feeling of pressure. The yardstick of frequency is whether the patient can sit through a movie, a church service, or ride in a car. By urinary urgency is meant sudden desire to void, amounting at times to incontinence. The pressure sensation is midline and right over the bladder. The feeling is one of downward pressure as compared to the falling-out sensation of prolapse.

The patients in this series also complained of nocturia, terminal tenesmus, and small stream. Three in the group had coughing incontinence from associated relaxation of the pelvic fascia. Of the eighteen pa-

tients complaining of nocturia, only three were troubled more than once a night. This is emphasized as nocturia is not characteristic of the condition.

TABLE I

COMPLAINT	NO. GIVING COMPLAINT
Urinary frequency	64
Urgency	24
Burning	23
Nocturia	16
Pressure	13
Terminal tenesmus	6
Coughing incontinence	3
Small stream	1

The etiology of this condition is obscure. Age has no connection with it, as is seen when the cases are broken down into age groups.

TABLE II

AGE	NUMBER
21-30	20
31-40	26
41-50	18
51-60	19
61 on	16

Childbirth and the resulting relaxation of the pelvic fascia is not a factor, for 50 had children and 50 did not.

Associated gynecologic difficulties do not cause the irritable vesical neck in view of the paucity and variety shown in Table III. If cervicitis

TABLE III

Fibroid	3
Prolapse	4
Cystocele	5
Rectal polyps	1
Trichomonas vaginitis	1
Pruritus	1
Cervicitis	1

were a cause of any importance, one would expect more cases listed. Cystoceles account for the three cases of coughing incontinence. The absence of gynecologic pathology in this group of 100 cases came somewhat as a surprise, as the general impression seems to be that the etiology is in the gynecologic tract.

However, previous gynecologic treatments and surgery may be an etiologic factor. In many such cases there is retention of urine with resultant infection of varying degrees which causes irritation. Sixteen of this series had previous laparotomies; 5 had had repairs; 4 had had x-ray treatments; and 2 had had radium.

Three patients stated that intercourse aggravated or caused recurrence of the difficulty; however, two of these had hypospadia of the

urethra. One should also add that the symptoms are worse in the morning and are aggravated by menstruation, although no statistics were kept on these two points.

As previously stated, objective findings are few. Only 4 patients had urethral caruncles, and 4 more had reddening of the meatus. If chronic urethritis and trigonitis cause caruncles and the irritable vesical neck, one would expect more caruncles and meatitis. It is possible that these patients were seen too early in the disease for such findings to be apparent. Two patients had gross urethral strictures, i.e., a 20 sound could not be passed without effort and resultant bleeding.

Cystoscopy was done only when the condition was resistant to treatment or when the duration of symptoms led one to feel that it would be wise to check at once. The major positive finding was chronic urethritis. By this is meant, red ridges starting at the vesical neck and running down the urethra. Table IV gives the findings.

TABLE IV

Chronic urethritis	5
Negative	4
Radium reaction	1
Polyps at bladder neck and in urethra	2

Treatment for all of these patients consisted of gradual dilatation of the urethra with Walther dilators and instillation of some medication. Eighty-four had a 5 to 10 per cent Gomenal* in olive oil, while 16 had 1 per cent silver nitrate. The silver was used in the more resistant cases. Only 11 had oral medication, 9 prontylin, and 2 Ammon. mandelate, for infection flared up or caused by treatment. In general, the patients were treated once a week until improvement was apparent, when the interval between treatment was doubled each time.

Dilatation was usually carried to 28 (French). When carried to the larger sizes, as 36, temporary incontinence resulted, and we rarely go so high now as it does not seem necessary to obtain results. The majority of the patients required three or four successive treatments to obtain relief of symptoms.

TABLE V

NO. OF PATIENTS	TREATMENTS TO OBTAIN RELIEF
7	1
11	2
17	3
12	4
6	5
3	6
4	7

*Gomenal, an ethereal oil from a plant, *Melaleuca viridiflora*, germicidal without irritating effects.

The two patients who had polyps were treated by electrocoagulation.

Some of this series is of recent date; however, forty patients were followed over a period of nine years, and it was found that the average number of treatments a year to maintain normal function and comfort was two. It is important that these patients realize that they are only being relieved, not cured.

The results are tabulated as "good," "improved" and "not helped." The "good" group are functioning normally, while the "improved" group are not satisfactory in all particulars. Ninety-eight of the 100 were followed up.

TABLE VI

Good	75	(4 wear rings for cystocele and prolapse)
Improved	18	
Not helped	5	

In conclusion, 75 out of 100 patients with irritable vesical neck were returned to normal function by dilatation of the urethra and instillation of medication. So simple a measure should be more generally used.

561 UNIVERSITY AVENUE

PERINEAL REPAIR WITH NONABSORBABLE SUTURE AND POSTOPERATIVE SITZ BATHS

A. P. HUDGINS, M.D., CHARLESTON, W. VA.

I DESIRE to comment on the favorable results which have followed the employment of nonabsorbable suture in perineal repairs, using, in addition, as postoperative treatment, sitz baths in hypertonic salt solution. Obstetric cases were the first to be given this type of treatment and the outcome was so satisfactory that it was used in routine perineal repairs on the gynecologic service.

Patients who had received other postoperative perineal care stated that they preferred this procedure because it was more comfortable and cleaner.

The method to be discussed includes the use of (1) nonabsorbable sutures by a method which permits their easy removal, and (2) the arrangement of a sitz bath which is both comfortable and effective.

The theory prompting the trial of this method resulted from the necessity of treating contaminated perineal wounds. For example: A patient with a tear from a home delivery was brought in about two or three hours after delivery, unshaven and contaminated, for hospital repair. This is a typical illustration and the results in these cases were satisfactory.

Hypertonic salt solution was used because any serum or fluid present would be drawn out of the wound. The deep sutures protruded through at the wound edges and thus allowed the escape of serum or blood, thereby preventing edema or hematoma and minimizing the possibility of infection.

The sitting posture also allows any serum or blood which may be in the vagina to be expelled. The vagina runs downward and backward and holds, as a cup, any serum or blood if the patient remains on her back. Theoretically, at least, the erect posture allows this to be evacuated, thus preventing an undesirable culture medium for bacterial growth.

The advantages of this routine are:

1. Nonabsorbable sutures permit removal of the suture, leaving no foreign bodies or knots which may cause pain or other trouble.
2. Sitz baths:
   - A. Reduce the possibility of infection and disruption of the wound.
   - B. Aid in the prevention of edema and swelling of the wound.
   - C. Increase patient's comfort and sense of cleanliness.
   - D. Are applicable in dirty or contaminated cases with vulva infection or when the wound is potentially infected.
   - E. Facilitate nursing care, because there is less odor and beds are less soiled.

Summarized, this means greater assurance of satisfactory healing and a more comfortable post-partum course.

Technique

After the episiotomy or the usual perineal dissection (in which the vaginal mucous membrane should be left attached to the underlying fascia), the upper point of the mucous membrane wound edge is caught with a clamp. The suture is put in about one centimeter above this point and tied loosely, as if being tied over the little finger. The mucous membrane edges are then approximated by a running quilt suture. This everts the edge of the mucous membrane and approximates a larger surface of the underlying fascia, which is really the supporting structure. This suture is carried on down and used to approximate the skin surface after the deep sutures have been put in.

The mucous membrane suture is stopped at the vaginal outlet and the deep sutures are put in. These deep sutures consist of two figure-of-eight and one single loop suture at the vaginal orifice.

The figure-of-eight sutures are put in with the deep loop for the muscle layer and the outer loop for the fascia coming out at the skin edge. They are tied with not too much tension.

The suture at the orifice of the vagina is put in in the usual manner. A large heavy needle is used; the muscles are caught well up in the labia majora, then coming back to the skin edge. Re-thread the deep end of the suture and repeat on the opposite side.

The running-quilt (or mattress) suture from the vagina is then continued down after the deep sutures are in place and tied. The edges of the skin are everted, which brings a larger fascia surface together and results in a stronger wound.

Before tying the skin suture a cork is placed in a loop, to be removed in twenty-four hours when swelling begins. If tied tightly at the time of operation, the sutures may cut into the skin and become painful.

The ends of all sutures are tied together and left long to facilitate removal. This group of suture ends is kept away from the rectum by tucking them through a loop of the suture near the vaginal outlet.

The skin is carefully avoided in placing the deep sutures, because the pressure exerted on nerve endings of skin definitely increases the pain. They are tied at the skin edge making them available for removal by clipping there.

The repair of the perineum is made entirely with a heavy nonabsorbable suture. It should be heavy to prevent the possibility of breaking and remaining deep in the perineum. Number 8, 10, or 12 white cotton has been found entirely satisfactory, though the other types of sutures have been used and no disadvantages found.

The sutures must be put in so that all can be removed easily and completely. Also, it has been found advantageous to allow the deep sutures to come through the skin edge thus acting as a wick.

Fig. 1.

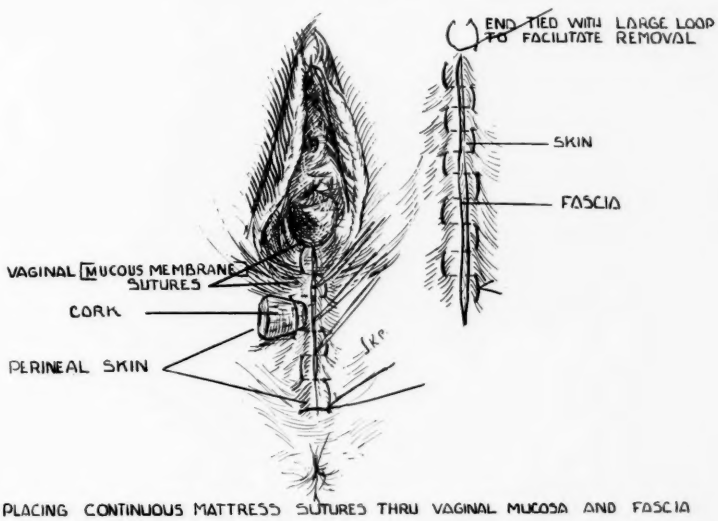

Fig. 2.

The sutures are usually removed the eighth day. If the skin sutures are causing discomfort they may be loosened earlier. The deep sutures, though usually removed before the patient leaves the hospital, have been left in for three weeks or more without harmful effects.

Early rising and "getting into the tub" is a mental hazard for the patient and may prove a handicap to be overcome at first. This problem disappears quickly, however, when results are observed.

The treatments were at first given in the regular bath tub. The water was limited to one or one and one-half inches and about 6 ounces of salt added. Heat was maintained by adding hot water as the solution cooled.

The movable sitz bath chairlike tub, devised for this type of treatment, makes the procedure simpler because it can then be given in the room and will not congest the bathroom facilities.

An improvement has been worked out in the mechanics of the equipment used.

A chair has been devised with a basin type seat to hold the solution. This can be moved to the patient's room. The tilt of the chair has been so arranged that the weight is kept off the painful perineum. A smaller amount of water can be used, thus assuring an adequate concentration of salt.

A heating device to maintain the desired heat of the solution has been worked out which has not been available in the other equipment. This adds to the comfort of the patient as well as the efficiency of the treatment (Fig. 3).

Coarse barrel salt (ice cream salt, rock salt) has been found to be less irritating than the more refined table salt, perhaps because of the magnesium carbonate or other chemicals added to make table salt flow more easily. In addition to the salt, vinegar (about 6 ounces) has recently been used. Karnaky claims that vaginal wounds heal more quickly in acid solutions.

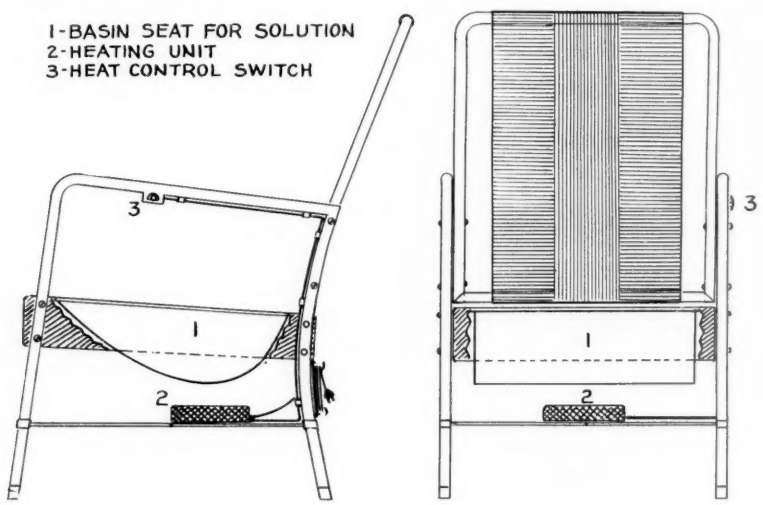

Fig. 3.—Sitz bath chair with heating device.

This type of operation with some modifications has been used on 41 obstetric and 48 gynecologic cases, which have been followed through for end results. (About 50 more cases have since been added to the series with equally good results.)

The results have been uniformly good. There was only one disruption of the perineal wound. This occurred in an obstetric case with many complications, including a temperature of 104° F. due to an acute respiratory infection preceding delivery. There was a stillborn-deformed child and an extention of the episiotomy to the rectal sphincter. The wound granulated well but did not heal by primary union. Hypertonic vaginal compresses were used instead of sitz baths in this case, due to the complicating respiratory infection and fever.

In one case a suture inadvertently was placed through the rectal mucosa and by error was allowed to remain. Some infection resulted in the perineum, but the drainage cleared up and healing was satisfactory.

There was one case of definite puerperal infection which developed. This woman was not a good surgical risk because of poor hygienic condition, poor nutrition, and anemia. The error could quite easily have been a break in technique other than in the postoperative care.

There was one case of an unexplained elevation of temperature starting on the eleventh day after delivery. There was no evidence of localized pelvic infection found. This must, of course, be considered a puerperal infection.

The advantages of early rising after operations have been brought forth and explained on several occasions. Allowing the patient up in a chair or on the side of the bed adds much to the comfort, and according to statistics reduces the postoperative complications of a respiratory and vascular nature.

It is striking how much more quickly the patient has a normal, healthy color and appearance following this early rising, and how much more quickly they overcome the postoperative shocked appearance.

One must, of course, be convinced of the efficacy of early rising to take full advantage of the sitz bath. Hypertonic hot compresses may be used but have not been found to be as effective as the sitz bath.

THROMBOCYTOPENIC PURPURA

DAN PHYTHYON, M.D., AND ROBERT E. LARTZ, M.D., SHARON, PA.

THROMBOCYTOPENIC purpura is a rare complication of pregnancy. The following case report concerns a seven months' pregnancy in a primipara in whom symptoms and laboratory studies were typical of thrombocytopenic purpura.

B. Z., a white, married woman, 28 years of age, para o, gravida i, was admitted to the Christian H. Buhl Hospital Aug. 19, 1942, approximately seven-months pregnant with the complaint of bleeding from the gums for four days, an increasing number of small purple spots over the extremities and back, and bloody urine for the past twelve hours.

Her last menstrual period was Jan. 8, 1942. The early pregnancy was uneventful with the exception that she bruised easily after any slight contusion. There was no family history of hemorrhagic diathesis. Her past history was uneventful except for an appendectomy two years ago.

Inspection on admission revealed a well-nourished and well-developed female. The skin of the extremities and back was covered with many small red purple spots. The head was negative except for bleeding of the gums and clots of blood at the tooth line. The abdomen was enlarged to a seven months' pregnancy; fetus was in a vertex presentation, fetal heart 130, in the L.L.Q., and height of the fundus was 25 cm.

Blood studies on admission showed a secondary anemia, leucocyte count and differential normal, coagulation time normal, bleeding time increased, a noncontracting clot, and platelet count of 68,000. These findings substantiated a diagnosis of thrombocytopenic purpura.

On the day following admission, 500 c.c. Type A citrated whole blood was transfused without reaction. The condition of the patient remained the same. Her gums continued to bleed and the urine contained free

blood. Four days after transfusion there were 66,000 platelets, and bleeding time was ten minutes twenty seconds.

A second transfusion of 250 c.c. of citrated whole blood was given August 25. Three days later the gums stopped bleeding and the urine began to clear. At this time there were 76,000 platelets. Bleeding time was five minutes thirty-five seconds.

A third transfusion of 300 c.c. of citrated whole blood was given September 1, and three days later the platelet count increased to 100,000, while the bleeding time was normal.

During the stay in the hospital, the fetal heart sounds remained good at a rate of 130 to 140. The petechiae began to fade and no new petechiae formed. All gum bleeding stopped and the urine was clear of blood.

Transfusions were withheld for eight days and on September 9, the laboratory work was repeated. The platelets had fallen to 68,000 and bleeding time increased to ten minutes, thirty seconds.

At this time there appeared to be two courses of treatment: To continue frequent transfusions, or to consider splenectomy. It was believed that the baby would not be viable, and it was estimated at about three pounds. In continuing transfusions there would be the risk of transfusion reaction and little change in the course of the disease. However, in performing the splenectomy with the seven months' pregnancy, there would be the risk of labor following the operation.

A fourth transfusion of 400 c.c. of citrated whole blood was given September 9. The patient was started on corpus luteum, 2 c.c. every eight hours, and after the third dose the splenectomy was performed September 12. There was minimal bleeding at the time of the operation, and the patient was returned to her room in good condition. The fetal heart was heard for forty-eight hours after the operation. The postoperative course was uneventful. Morphine, gr. $\frac{1}{4}$, was given on two occasions after the operation with pantopon, gr. $\frac{1}{3}$, on three occasions.

No fetal heart sounds were heard after September 14. The laboratory reported 168,000 platelets and normal bleeding time on September 15.

Labor began the next day and after three hours of moderate pains the cervix was fully dilated and the patient was delivered of a stillborn, slightly macerated female child, by low forceps under gas-oxygen anesthesia. The placenta separated in four minutes and was expressed with minimal bleeding. Intravenous ergotrate was used following the third stage. The placenta was complete and normal. The infant weighed three pounds and four ounces.

The abdominal incision was examined following the delivery and was found to be intact. The skin clips were removed on the following day. There was no abnormal flow of lochia.

On September 24, twelve days after the splenectomy, there were 340,000 platelets. At the time of discharge from the hospital there was no recurrence of bleeding or petechiae.

Pathologic Report.—The spleen measured 13 by 11 by 5 cm. Sections revealed no pathology in the lymphoid follicles. The splenic pulp, however, had an increase in fibrous connective tissue stroma. There were many destroyed red blood cells and the red cells were accumulated in the various parts of the spleen.

Diagnosis: Hyperplastic spleen.

Follow-Up.—Four months after operation the patient was in good health. Menses were regular every four weeks, and flow lasted five days. A blood study on Jan. 21, 1943, revealed 241,000 platelets, normal bleeding and coagulation times, 4,160,000 red blood cells and 8,500 white blood cells.

The splenectomy was performed by Dr. C. H. Moses of Sharon, Pa.

Summary

A case of thrombocytopenic purpura complicated by a seven months' pregnancy is presented. Frequent transfusions were given without evident clinical improvement. A splenectomy was performed without disturbing the pregnancy. Liberal amounts of corpus luteum were given as pre- and postoperative treatment. However, on the fourth postoperative day, the patient was delivered of a premature stillborn infant following a four-hour labor. The postoperative course was otherwise uneventful.

Ricci, G., and Balaguer, M.: Placental Blood: Its Indications in Gynecology, Bol. Soc. de obst. y ginec. de Buenos Aires **20:** 850, 1941.

The authors treated with placental blood women who had the following ailments: 32 adnexal disturbances, 7 metropathies (3 juvenile and 4 pre-eclimacteric), 1 puerperal pyelitis, 1 essential dysmenorrhea, 2 puerperal endometritis, 2 pelvic congestions, and 5 inductions of labor.

The placental blood is collected aseptically immediately after birth and preserved in equal parts of a solution of sodium citrate 5, sodium chloride 9 and redistilled water to 1,000. Small transfusions of blood or serum, not exceeding 20 c.c. per day, are given in series of 6 to 10. Lately, serum transfusions have been preferred. The patient is kept in the clinic until the danger of posttransfusion reactions has passed.

Nearly all adnexal cases were chronic or subacute with lesion of one or both adnexa, palpable tumor, pain and menstrual disturbances. They presented two types of reaction to the transfusion: one was inconstant and of the posttransfusion type, and the other was localized in the genital apparatus. The focal reaction, which the authors regard as specific, consists of increase in local pain and size of the involved part, general ill-feeling and fever, sometimes exceeding 38° C. This reaction disappears after a few hours. The result is disappearance of pain and return of general well-being. Menstruation becomes regular, the size of the uterus decreases and the discharge and tumor disappear. In recurrence the treatment is repeated and gives good results. Rebellious cases are those which have received insufficient treatments: even in these, a series of transfusions may be an excellent procedure during the preoperative stage. In menstrual disturbances, the possibility of ectopic pregnancy must always be eliminated before treatment is started. Treatment was ambulatory in most cases.

Results were good in the cases of metropathy, pyelitis and endometritis, but were not definite in dysmenorrhea and pelvic congestion in which a longer period of observation is necessary to allow drawing final conclusions. There were two successes and three failures for induction of labor.

J. P. GREENHILL.

Editorial

CAUDAL ANESTHESIA IN OBSTETRICS

ATTEMPTS to relieve the discomforts and, what are generally designated as the "pains" of labor, have constituted an ambitious project for clinical research, particularly since the middle of the last century when Sir James Simpson advocated inhalations of chloroform for this purpose. He preferred the latter to ether as more readily administered and, in his belief, less dangerous, only to meet with the extended opposition of many members of the medical profession as well as the clergy. The risks of even this comparatively simple procedure, however, came to be recognized and in 1880 Klinkowitch, of St. Petersburg, proposed that nitrous oxide be given intermittently with each "pain."

The admitted disadvantages and occasional dangers associated with most inhalation methods stimulated the introduction in 1902, by Kroenig and Gauss, of the widely heralded "twilight sleep," which depended on the combined hypnotic and amnesic effects of morphine and scopolamine. This was hailed as the *sine qua non* of satisfactory obstetric deliveries, and through the medium of the lay press generated a public demand on physicians for its universal employment. The fact that many babies were asphyxiated in greater or less degree stimulated further search for an ideal, and a succession of sedative drugs specifically directed to the relief of labor pains appeared on the medical horizon. To oral and hypodermic administration an approach through the spinal canal has been added in more recent years based on experiences in general surgery. Solutions of the cocaine derivatives have been employed for this purpose, and now the effort is to limit the field to the sacral and lumbar plexuses by continuous bathing of nerve trunks with the anesthetic through the medium of the peridural space.

It is claimed by Hingson and Edwards in a recent article* that the analgesia developed by their special technique is safe for both mother and child, and in this report they describe their observations in a large series of cases (589) conducted in various places either by themselves or under their supervision, with almost universally satisfactory results. Following this, in the same journal, is a preliminary report by two other investigators† of a much smaller series in which, however, the disadvantages and contraindications are more clearly enumerated. These should be carefully studied by those who may undertake to employ the

*J. A. M. A. 121: 225, 1942.

†Gready, T. G., and Hesseltine, H. C.: Ibid, p. 229.

procedure. In an accompanying editorial in the same journal, there are presented laudatory opinions by other observers but likewise the caution that its employment is limited to hospitals and to a carefully trained personnel.

Due and respectful consideration must be accorded to any reasonable proposal which has for its object the alleviation of the "pains" of labor. For women no longer regard these as necessary or inevitable accompaniments of childbirth. It is essential, however, that such measures be safe and practical, and it is by this yardstick that they should be evaluated.

It has been demonstrated that the anatomy of the sacral hiatus is subject to variations as is the capacity of the canal. Injury is likely and the fairly large doses of the anesthetic agent used are also fraught with danger because the individual susceptibility of the patient cannot readily be determined in advance. All of these facts must be carefully determined before any general adoption of the procedure can be permitted.

Enthusiasm for a new procedure is natural when this is based on favorable personal experience. Nevertheless a sense of balance and proportion must always be maintained in passing final judgment. In this instance apparently insufficient thought has been given to the fact that the invasion of the delicately constituted spinal canal is essentially a major procedure, often fraught with risk and uncertainty. The question may well be asked whether this is necessary to compensate the average, normal parturient for what in most instances are discomforts quickly forgotten and leaving little or no disturbance in their train.

The account of a labor conducted under the method advocated by Hingson and Edwards is captivating. There is, however, little stress laid on the disturbing factors which should be noted in the succeeding article by Gready and Hesseltine. Whether it can or should be applied in a routine manner in all cases, as apparently practiced by the original authors, is open to serious question. It seems unfortunate that the recent wide newspaper publicity may lead to false hopes among pregnant women as to the practicability and safety of a procedure which must be subjected to a longer period of observation by the trial-and-error method together with an impartial interpretation of results, otherwise even a few serious accidents may condemn what might prove a valuable addition to our obstetric armamentarium in selected cases. In this connection attention is directed to another contribution on the subject in the present issue of this JOURNAL.

Department of Reviews and Abstracts

Selected Abstracts

Gynecology—Pathologic and Hormones

Dutra, L. H.: Vaginal Cysts, Rev. de ginec. e d'obst. **36:** 75, 1942.

The author reports a series of seven vaginal cysts in four patients. He operated upon these women and found that all the cysts were of Wolffian origin. The epithelia of the cysts varied in type. The author emphasizes that during operation bleeding is profuse, chiefly because there is no good line of cleavage between the cyst wall and the vaginal mucosa.

J. P. GREENHILL.

Borras, P. E., Alvaro, J., and D'Acquila, H.: Chorionic Villi Retained and Enclosed in the Uterine Muscle, Bol. Soc. de obst. y ginec. de Buenos Aires **20:** 829, 1941.

The authors report four cases where villi were found within the uterine musculature. In one the villi were enclosed in the myometrium without any tumor formation, but in the other three the villi were found in uteri with interstitial, submucosal, and subserosal fibromyomas, respectively. There was a considerable interval between the last pregnancy and the appearance of menstrual disturbances in three patients (from six months to four years), showing that villi can be retained for a long time without causing disturbances or without proliferating. It might be thought that the symptoms were produced by the fibromas only and that the villi had not influenced the clinical picture. However, histologic examination showed that the Langhans cells had undergone no regression and that their protoplasm and nuclei were fully alive.

In the first patient, who was admitted quite some time before the menopause, the disturbances could hardly have been due to the fibroma; therefore, a degenerating neoplastic process was suspected, and it was only after histologic examination that the authors realized the symptoms were caused by the villi enclosed in the fibrous mass. In the second case the last pregnancy dated back seven years and the menstrual disturbances appeared gradually four years later until intervention became necessary. In the third patient, the free interval had been short but distinct. The Friedman test was negative and section of the specimen showed that the bloody nucleus in the myometrium was encapsulated and easily detached from the muscular wall. Histologically, the mass of villi was separated from the muscle by a heavy layer of fibrin, which explains the result of the Friedman test; the Langhans cells and plasmodium were regressing. The fourth patient was 40 and had had 16 pregnancies with 13 living children, the last birth having been two years previously. Menstruation had become gradually irregular and examination revealed a soft myoma of the fundus.

It seems reasonable to suppose that inclusions can occur in foci of endometriosis, but it is difficult to explain why the villi which have naturally an invasive character,

remain inactive for long periods. Probably the organism must acquire a predisposition to allow these tissues of fetal origin to develop in it. The diagnosis offers great difficulties and operation is always indicated because of the danger presented by retention of these remnants. The Friedman test after operation was negative in all four patients.

J. P. GREENHILL.

Bottiroli, Ernesto: Repeated Hydatidiform Mole, Bol. Soc. de obst. y ginec. de Buenos Aires **20:** 847, 1941.

The author calls attention to the extreme rarity of this disorder; only one case is found in the Argentine literature. Extirpation of any uterus that has contained a mole is recommended by those who regard the mole as a malignant degeneration, in opposition to those who consider it a benign process. The author reports a case in a woman, aged 41 years, who had three molar pregnancies interspersed between six normal ones. The fifth, sixth, and eighth pregnancies were undoubtedly molar; the author attended to the last two and, when showing the vesicles to the patient, was informed that she had expelled exactly the same kind of material during the first. The distribution of these molar accidents between the fourth, seventh, and ninth pregnancies which were normal favors the theory of the ovular origin of the disorder. Hormone studies made during the third molar pregnancy revealed the same amounts as in normal pregnancy. With Brindeau, the author thinks that this absence of increase in hormones is due to the fact that the mole has ceased to grow and was simply in the stage of retention.

J. P. GREENHILL.

Dahl-Iversen, E., Hamburger, C., and Jorgensen, H.: Cystic Glandular Hyperplasia of the Endometrium Elucidated by Therapeutic Experiences in Patients and by Experiments on Rhesus Monkeys, Acta. obst. et gynec. Scandinav. **21:** 215, 1942.

Therapeutic tests carried out by the authors showed that it is not practical by simulative therapy to cure cystic glandular endometrial hyperplasia in young women even with doses up to 42,000 international units of chorionic gonadotropin. This type of treatment merely produces a temporary reduction of the menses. After this there is a relapse. There appear to be no difference in substitutional therapy and stimulation treatment. In young girls the estrogens have no effect whatsoever.

Experiments revealed that chorionic gonadotropins are capable of producing physiologic changes in Rhesus monkeys but these are temporary. After treatment is discontinued, the ovaries resume their normal function.

Administration of estrogens for a sufficient length of time produces changes in the monkey that have some morphologic resemblance to cystic glandular endometrial hyperplasia in the human. However, the symptoms which appear in the human being are absent, namely, hemorrhage and necrosis.

J. P. GREENHILL.

MacBryde, Cyril M., Castrodale, Dante, Helwig, Elson B., and Bierbaum, Olga: Hepatic Changes Produced by Estrone, Estradiol, and Diethylstilbestrol, J. A. M. A. **118:** 1278, 1942.

Dogs were used in this experiment, and they were given equal quantities of estrone, estradiol benzoate, and diethylstilbestrol dipropionate which were compared on an equal standard (international unit). The hepatic changes that occurred consisted of fatty degeneration and hydropic degeneration. Alterations in the parenchymal cells were not prominent. The bone marrow showed a variable degree of hyperplasia

chiefly of the myeloid elements. The degree of maturation of the myeloid cells varied. The same response was produced by each of these drugs in the peripheral blood. There was a leucocystosis and a fall in thrombocytes. There was a moderate decrease in red blood cells and hemoglobin. The authors finally conclude from their study that, when, given to dogs, large doses of the natural estrogens and estradiol produce hepatic changes indistinguishable from those produced by diethylstilbestrol.

WILLIAM BERMAN.

Miescher K., and Gasche, P.: Lingual Application of the Female Sex Hormones, Schweiz. med. Wchnschr. **72:** 490, 1942.

The authors studied the lingual application of estradiol on the uterus of castrated albino rats. They observed that solutions of estradiol produced a reaction in the uterus which was 10 to 20 times as great as the oral application of this substance. In fact the lingual application of estradiol produced some effects which could not be obtained with oral injection. The authors point out a parallel between the lingual use of both the male and female hormones.

J. P. GREENHILL.

Freed, S. C., Eisis, W. M., and Greenhill, J. P.: The Therapeutic Efficiency of Diethylstilbestrol Esters, J. A. M. A. **119:** 1412, 1942.

The authors propose a method for determining the potency of estrogens by using the subjective response of menopausal women. Only patients with moderate or severe symptoms including at least two to four hot flushes were used for testing. For the estrogens that were administered by injection, a technique was adopted whereby the length of the period of relief following the last of a series of injections was used as an index of the therapeutic efficiency of the estrogens. Three compounds were used: diethylstilbestrol, diethylstilbestrol dipropionate, and diethylstilbestrol dipalmitate. The minimal effective dose of the dipalmitate is 50 times greater than plain diethylstilbestrol.

It was found that the diethylstilbestrol was inferior to the dipropionate in efficiency since the period of effective relief is less. The dipropionate was effective on an average of five weeks. The dipalmitate was more effective than either of the other two, its effect lasting an average of nine to ten weeks.

The dipropionate is considerably less toxic than the free compound. The dipalmitate is practically free from toxicity.

WILLIAM BERMAN.

De Lisi, Giuseppe: Observations on Short Wave Therapy in Gynecological Infections, Rassegna d'ost. e ginec. **49:** 463, 1940.

The author reports on the experimental use of short wave therapy in a series of 80 patients, who presented varying degrees of pelvic inflammatory disease. Thirty-one of the patients received the treatments during the ambulatory phases of their illnesses. The number of treatments, per patient, varied between 3 to 20 with an average range of 10 to 20 treatments for each course. Each treatment lasted seven to twenty-five minutes and was given either daily or upon alternate days. The patients received medical therapy in addition (vaccines, colloidal metals, and other drugs).

The author concludes that short wave therapy, as a therapeutic adjunct, is valuable. It is harmless in application, assists materially in reducing the pain and tends to cause earlier regression of acute pelvic inflammatory disease. He states that active febrile reactions and menorrhagia upon an inflammatory basis do not constitute contraindications.

CLAIR E. FOLSOME.

Mussio-Fournier, J. C., and Albrieux, A.: The Absorption of the Sex Hormones by the Skin. (Discussion of a Case of Facial Hypertrichosis Relieved by Intradermal Injections of Folliculin), Presse méd. **48:** 569, 1940.

The authors report that the masculine or female hormones, when applied to the skin in an ointment or in alcohol or oily solutions, are absorbed locally by the skin and produce their characteristic reactions. In a case of facial hypertrichosis locally applied folliculin produced a loss of hair while the controlled side of the face continued to evidence hypertrichosis. Three photographs are offered in the evidence submitted. It was interesting to observe that the patient, described in this report, gave a history of hypomenorrhea with periods of secondary amenorrhea preceding and during the development of the hypertrichosis.

CLAIR E. FOLSOME.

Wilkinson, R. J.: Chronic Pelvic Disease Resulting From Childbirth Improved Operative Technic, South. Surgeon **11:** 359, 1942.

The author was impressed with the large number of patients with pelvic complaints who attributed their symptoms to antecedent childbirth. In a series of 246 such patients with chronic pelvic disease uncomplicated by associated tubal abnormalities, fibroid tumors, ovarian cysts or procidentia, there was no response to office treatment, and surgical corrective procedures were employed. The usual complaints were vaginal discharge, backache, disturbed menstrual function, lower abdominal pain and nervousness; the common pelvic findings were an enlarged, retroverted uterus, broad ligament varicosities, endocervicitis, and perineal lacerations. All of these patients had a vaginal repair and cervical dilatation and conization, and, in 242 subtotal hysterectomy with ligament shortening was performed. No fatalities occurred. There were 167 replies to a questionnaire sent two to four years after operation. Ninety-three per cent felt that the surgical repair was beneficial; 56 per cent were still menstruating, and the members of this group obtained the greatest relief from all symptoms. The observation that relatively few patients in whom some of the endometrium was retained require estrogen therapy, impressed the author with the importance of performing defundation, and it strengthened his belief that there is a uterine hormone.

Careful postnatal check-up examinations with early institution of corrective treatment will prevent the development of more extensive pelvic abnormalities. Later, conization of the cervix and vaginoperineal repair may be all that is required. When more extensive changes have occurred, the additional performance of defundation with ligament shortening is advocated. For the patient 40 years of age or older, panhysterectomy is the procedure of choice.

ARNOLD GOLDBERGER.

Ovarian Neoplasms

Weed, John C., and Collins, Conrad G.: Cystic Degeneration of the Ovaries, Surgery **11:** 292, 1942.

On the basis of extensive experiments on animals the writers arrive at the following conclusions: (1) Cystic degeneration of the ovaries, formerly thought to be the result of chronic infection, is now variously ascribed to sympathetic dysfunction and hormonal imbalance. Circulatory impairment is an infrequently considered but important etiologic factor. (2) Circulatory impairment was produced in the ovaries of 18 rabbits and one dog by either vascular ligation or artificial

prolapse. Sections of these ovaries showed changes in the follicular apparatus analogous to those found in human ovaries with cystic degeneration. (3) Partial resection and suspension of such ovaries yielded the best results.

HUGO EHRENFEST

Castro Barbosa, J.: Simultaneous Torsion of Bilateral Dermoid Ovarian Cysts, Rev. méd. munic. (Rio de Janeiro) **1**: 207, 1941.

A 27-year-old woman with a normal menstrual history noted, at her last period, a decrease in amount and change in color. Eighteen days later she was taken with generalized lower abdominal pain soon followed by nausea, vomiting, and a sense of fullness in the lower abdomen. On examination there were hyperesthesia over the iliac fossae and some defensive spasm on the right. Rectal and vaginal examination revealed tenderness in both iliac fossae and on the right a mass separate from the uterus was made out. Puncture of the cul-de-sac disclosed blood and the patient was subjected to laparotomy with a diagnosis of ruptured ectopic pregnancy. Bluish congested ovarian tumors were found on both sides, each one twisted twice on its pedicle. These were removed and the patient made a normal recovery. With the appearance of menopausal symptoms, the author has announced his plans to implant an ovary of a woman of similar blood group in the patient's uterus.

R. J. WEISSMAN

MacFee, William F.: Benign Tumors of the Ovary Associated With Ascites & Pleural Effusion, Ann. Surg. **113**: 549, 1941.

The author reports a case of multiocular cystadenoma of the ovary associated with ascites and pleural effusion, which constitutes an exception to the type of ovarian tumor which has ordinarily been associated with this complication. The predominant physical symptoms were related to interference with proper aeration, and the physical findings were similar to those observed in cases of ovarian fibroma with ascites and pleural effusion. Ablation of the tumor and removal of the pleural fluid likewise terminated the disease.

WILLIAM BERMAN

Heller, J.: Floating Ovarian Cystadenoma, Zentralbl. f. Gynäk. **64**: 1231, 1940.

A 24-year-old virgin noted daily gradual and painless abdominal enlargement. A diagnosis of inoperable carcinoma of the liver was made in one clinic and the woman received 5 series of deep roentgen therapy, without relief. There was nothing unusual in the menstrual history. The past few months had been marked by anorexia, tachycardia, and effort dyspnea. Roentgenograms revealed only slight elevation of the diaphragm. On rectal examination a tumor was felt which appeared to fill the whole abdominal cavity. It was hard in consistency in the hepatic region and soft and fluid on the left side of the abdomen. In the genupectoral position, rectal examination revealed a small uterus forced to the left and a pedicle arising from it on the right. The abdominal fluid was emptied by trocar and a pseudomucinous cystademona was removed. The tumor and fluid weighed 31 kilos. The interesting feature of the case appears to be the importance of the knee-chest position in making the pedicle available to the examining finger. Previous physicians had been misled, according to the author, by the apparent location of the tumor, its displacement of the liver and the appearance of "liver spots" on the patient's skin.

R. J. WEISSMAN

Kny, Walter: Arrhenoblastoma, Ztschr. f. Geburtsh. u. Gynäk. **121:** 406, 1940.

Robert Meyer's classification of arrhenoblastomas is briefly reviewed. A case is described which belongs to the third type, the atypical, mostly solid form. The patient was a 66-year-old para vi. Menses were normal to menopause at the age of 50. She was admitted with the complaints of dyspnea, diarrhea for some months, swollen legs, and weakness. There had been increasing loss of hair from the head and a parallel growth of a beard. Clinical examination showed scanty head hair, a male beard, and no striking voice changes. Blood showed an anemia with attempts at new blood formation. The patient died seven days after admission.

Autopsy showed male distribution of pubic hair, considerable enlargement of the clitoris and striking atrophy of the breasts. The right ovary contained a firm elastic tumor 8 to 10 cm. in diameter, and the left, a similar tumor about 5 to 6 cm. in diameter. The uterus and tubes were markedly atrophic. Metastases were found in the lungs, thyroid, and widely disseminated in bones.

The ovarian tumors were made up for the most part of masses of spindle cell sarcomalike tissue. Toward the periphery, epithelial strands were found. The original description should be consulted for details of tissue variations.

The various theories of the origin of arrhenoblastoma are discussed.

J. L. McKelvey

Hohage, Erich: Report of a Case of Disgerminoma of the Ovary, Ztschr. f. Geburtsh. u. Gynäk. **121:** 401, 1940.

A tumor of the right ovary, the size of a man's head, was removed from a 17-year-old girl. She had never menstruated. She showed a somewhat hypertrophic clitoris, a male type of voice, heavy bone structure, and a light beard. Otherwise, she seemed to have female characteristics. The uterus and both tubes were markedly hypoplastic. The left ovary was the size of an almond and cystic. The urine contained only follicle-stimulating hormone.

Operation disclosed a tumor which is described as a characteristic disgerminoma. X-ray therapy was given, but in spite of this metastases developed in the lungs, liver, lymph nodes, and vertebrae. The patient died five months after operation.

J. L. McKelvey

Kazancigil, Laqueur, and Ladewig: Papillo-Endothelioma Ovarii, Am. J. Cancer **40:** 199, 1940.

The writers describe in detail the careful study of three malignant ovarian tumors which presented the same general picture of Schiller's "mesonephroma ovarii."

Their study, however, including a plastic reconstruction of one of these growths, failed to reveal evidence of a derivation from remnants of the primitive mesonephros. In view of the endotheliomatous character of the cells and the presence of angiomatous and angioendotheliomatous structures, they believe that these tumors are rather to be regarded as angioendotheliomatous neoplasms. The occurrence of accessory organ-specific components in two of the cases suggests an origin in a gonadal anlage. For this reason they propose for this group of ovarian tumors the name "papilloendothelioma."

Hugo Ehrenfest

Kleine, H. O.: Primary Ovarian Blastomas of the Adrenal Cortex Type, Zentralbl. f. Gynäk. **63:** 2249, 1939.

This is a brief summary of the present status of the knowledge of pelvic hypernephromas. The author points out that the tumor is seldom if ever primarily in the ovary so that the title is not accurate.

In a description of the embryology, it is pointed out that the anlage of the adrenal cortex develops at about four weeks, whereas the medulla does not appear until at least four weeks later. This apparently explains the frequency with which portions of the cortex reach the pelvis in association with the development of the internal genitals. An extremely small proportion of these develop tumors while most disappear with advancing age.

The tumor cells are characteristically those of the adrenal cortex. Three histologic forms are recognized in the tumor:

1. Closely placed parallel strands of cells.
2. Solid masses separated by connective tissue.
3. Occasional adenomatous, papillary, or cystic forms are reported.

The histology is characterized as well by marked vascularity, hemorrhages and necrosis.

It is a peculiarity of the tumor that it often, though not always, changes the sexual orientation of the host bringing about demasculinization of the male and defeminization of the female. The author believes that this is more likely than that sex reversal occurs. A hypothetical explanation of this loss of sex specificity is discussed. The author summarizes the 16 reported cases and adds two of his own.

J. L. McKelvey

Sammartino, R., and Herrera, R. G.: Myeloid Tumor of the Ovaries, Rev. méd. Latino-am. **25:** 284, 1939.

This is an unusual case because of the lack of symptoms referable to the disease and because the primary focus apparently was in the ovaries. A 35-year-old housewife, dying after an operation for a tumor of the cerebellopontine angle, was autopsied with the postoperative diagnosis of corticocerebeller arachnoiditis. The findings were negative except with respect to the myeloidosis. The uterus was small and atrophic with a few fibrous perimetrial adhesions. The ovaries were enlarged, ellipsoid, one measuring 8 by 5 by 3 cm., the other 7 by 5 by 4 cm. There were similar on section, the cut surface resembling a sectioned lymphatic gland. Medullary nodules were apparent, with a fascicular connective tissue. A few old corpora lutea and a condensed ovarian stroma were found at the hilus. The serous surfaces were pale, having a few superficial adhesions and a few cystic follicles. Microscopically the granulocytic series was well represented, with an abundance of eosinophiles. The pre-erythrocyte series was present in lesser proportion. A few microscopic foci were found in the kidneys and pancreas. There was a questionable infiltration of the meninges.

R. J. Weissman

Traut, Herbert F., and Marchetti, Andrew A.: A Consideration of So-Called "Granulosa" and "Theca" Cell Tumors of the Ovary, Surg., Gynec. & Obst. **70:** 632, 1940.

The Society of Gynecological Pathologists of New York has collected a group of 61 ovarian tumors which have been diagnosed as belonging to the group of neoplasms having their origin in the theca granulosa cell complex. The authors were appointed to study these tumors as well as the clinical data of the patients from whom they originated. The work is as yet incomplete; however, the material was found to yield information justifying a partial report at this time, with the following conclusions:

The use of Foot's silver stain makes possible the differentiation of theca from granulosa cells in most instances.

So-called granulosa cell tumors contain varying amounts of theca cell elements as well, so that pure granulosa cell tumors are rare. Most tumors contain from one-fourth to one-third of their differentiated cells in the form of theca cells. A number of tumors were encountered which had equal representations of the two cell types, while most so-called theca cell tumors also contained granulosa elements in considerable representation. One pure granulosa cell tumor and four pure theca cell tumors are described.

An attempt is made to outline the life cycle of these tumors and its relationship to the clinical syndrome they present.

WILLIAM C. HENSKE

Sailor, Seaton: Ovarian Dysgerminoma, Am. J. Cancer **38**: 473, 1940.

A malignant tumor of the ovary histologically similar to the testicular seminoma was originally identified by Robert Meyer as arising from indifferentiated sex cells of primitive mesenchyme. He named it dysgerminoma and emphasized its tendency to occur in young women and to its frequent association with hermaphroditic or pseudohermaphroditic states. A total of approximately 160 cases have so far been reported. This new growth most frequently occurs in the right ovary of women below the age of twenty.

The author reports five new cases: (1) A 10-year-old colored girl. A large left-sided dysgerminoma was removed; later deep x-ray therapy. About thirteen months later second laparotomy for large metastases in uterus, right tube, and ovary. Died seven months later. (2) A white girl, 18 years old. A firm, fixed large tumor removed from right side. Patient in excellent condition eight months after operation. (3) A white girl, 15 years old. Firm, semisolid tumor of right ovary removed. Patient, three years after operation, still in excellent health. (4) Colored girl of 17 years. Soft, oval tumor of right ovary removed. Six years later patient perfectly well. (5) White woman, 21 years old. Large firm tumor of right ovary extirpated. Patient in good health four years later, after delivery of her second child since operation was done.

HUGO EHRENFEST

Duran, Alfredo: Cystic Teratoma Infected by Eberthella Typhi, Bol. Soc. chilena de obst. y ginec. **4**: 415, 1939.

A 16-year-old girl, convalescing from an attack of typhoid fever several months previously, complained of severe intermittent pains in the right iliac fossa which became worse on lying down. She had dysuria, low-grade fever, and general malaise. At the menarche, at age of 15, there was a profuse flow of eight days' duration followed by a year of amenorrhea. Then scanty menses appeared every twenty-six days. During the two months of her illness the periods were ten and fifteen days long, respectively, the subsequent and last period being six days long.

A round tumor was palpable in the hypogastrium, occupying most of both iliac fossae and extending upward to the umbilical level. To confirm the previous diagnosis of typhoid, a Widal was done and found positive. After 26 febrile hospital days with no improvement, the patient was prepared for operation. Laparotomy revealed a pyriform cystic tumor of the left ovary, the superior pole adherent to the omentum, the inferior thoroughly adherent in the cul-de-sac of Douglas. When opened the tumor contained 1,500 c.c. of purulent fluid, from which the typhoid bacillus was cultured. Recovery was uneventful.

R. J. WEISSMAN

Item

American Board of Obstetrics and Gynecology, Inc.

The general oral and pathological examinations (Part II) for all candidates will be conducted at Pittsburgh, Pennsylvania, by the entire Board from Thursday, May 20, through Tuesday, May 25, 1943. The Hotel Schenley in Pittsburgh will be the headquarters for the Board, and formal notice of the exact time of each candidate's examination will be sent him several weeks in advance of the examination dates. Hotel reservations may be made by writing direct to the Hotel.

Candidates for *re-examination* in Part II must make written application to the Secretary's Office not later than April 15, 1943.

The Pittsburgh Obstetrical and Gynecological Society will hold an informal subscription dinner meeting at the Hotel Schenley, on Saturday evening, May 22, 1943, at 7:00 P.M. Visitors, here for the examinations, are cordially invited to make arrangements to attend. Reservations may be made by writing to Dr. Joseph A. Hepp, Secretary of the Society, at 121 University Place, Pittsburgh, Pa. An interesting program is being provided.

The Office of the Surgeon-General (U. S. Army) has issued instructions that men in Service, eligible for Board examinations, be encouraged to apply and that they may request orders to Detached Duty for the purpose of taking these examinations whenever possible.

Candidates in Military or Naval Service are requested to keep the Secretary's Office informed of any change in address.

Deferment without time penalty under a waiver of our published regulations applying to civilian candidates will be granted if a candidate in Service finds it impossible to proceed with the examinations of the Board.

Applications are now being received for the 1944 examinations. For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

American Gynecological Society. *President,* George W. Kosmak, New York, N. Y. *Secretary,* H. C. Taylor, Jr., 830 Park Ave., New York, N. Y. Annual meeting. (Cancelled.)

American Association of Obstetricians, Gynecologists and Abdominal Surgeons. *President,* W. R. Cooke, Galveston, Texas. *Secretary,* James R. Bloss, 418 11th Street, Huntington, W. Va. Annual meeting, September, 1943, Hot Springs, Va.

Central Association of Obstetricians and Gynecologists. *President,* John H. Moore, Grand Forks, N. D. *Secretary-Treasurer,* W. F. Mengert, Iowa City, Iowa. (Cancelled.)

South Atlantic Association of Obstetricians and Gynecologists. *President,* Oren Moore, Charlotte, N. C. *Secretary,* T. J. Williams, University, Va. Next meeting. (Cancelled.)

A. M. A. Section on Obstetrics and Gynecology. *Chairman,* L. E. Phaneuf. *Secretary,* Philip F. Williams, 2206 Locust St., Philadelphia, Pa. Next meeting. (Cancelled.)

New York Obstetrical Society. *President,* Henry T. Burns, *Secretary,* Ralph A. Hurd, 37 E. 64th Street, New York City. Second Tuesday, from October to May, Yale Club.

Obstetrical Society of Philadelphia. *President,* John C. Hirst. *Secretary,* James P. Lewis, 3815 Chestnut St., Philadelphia, Pa. First Thursday, from October to May.

Chicago Gynecological Society. *President,* Edward Allen. *Secretary,* Eugene A. Edwards, 104 S. Michigan Ave., Chicago, Ill. Third Friday, from October to June, Hotel Knickerbocker.

Brooklyn Gynecological Society. *President,* Samuel Lubin. *Secretary,* John J. Madden, 362 Washington, Ave., Brooklyn N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Avenue, Brooklyn, N. Y.

Baltimore Obstetrical and Gynecological Society. *President,* Lawrence Warton. *Secretary-Treasurer,* John W. Haws, 9 East Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Building.

Cincinnati Obstetrical Society. *President,* Edward Friedman. *Secretary,* Carroll J. Fairo, Cincinnati, Ohio. Third Thursday of each month.

Louisville Obstetrical and Gynecological Society. *President,* Layman A. Gray. *Secretary,* E. P. Solomon, Hegburn Building, Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.

Portland Society of Obstetrics and Gynecology. *President,* Howard Stearns. *Secretary,* William M. Wilson, 545 Medical Arts Bldg., Portland, Ore. Last Wednesday of each month.

Pittsburgh Obstetrical and Gynecological Society. *President,* J. L. Gilmore. *Secretary,* Joseph A. Hepp, 121 University Place, Pittsburgh, Pa. First Monday of October, December, February, April, and June.

Obstetrical Society of Boston. *President,* Thos. Almy, Fall River, Mass. *Secretary,* Paul A. Younge, 101 Bay State Road, Boston, Mass. Third Tuesday, October to April, Harvard Club.

New England Obstetrical and Gynecological Society. *President,* Frank A. Pemberton. *Secretary,* A. F. G. Egelow, 31 Maple Street, Springfield, Mass. Meetings held in May and December.

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*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL.

Pacific Coast Obstetrical and Gynecological Society. *President,* T. Floyd Bell. *Secretary-Treasurer,* William Benbow Thompson, 6253 Hollywood Boulevard, Los Angeles, Calif. Next meeting undecided, probably San Francisco, Calif., November 5-6, 1943.

Washington Gynecological Society. *President,* John Warner. *Secretary,* L. L. Cockerille, 900 17th Street, N. W., Washington, D. C. Fourth Saturday, October to May.

New Orleans Obstetrical and Gynecological Society. *President,* E. L. Zander. *Secretary,* Eugene Countiss, 921 Canal St., New Orleans, La. Meetings held every other month.

St. Louis Gynecological Society. *President,* S. A. Weintraub. *Secretary,* Joseph A. Hardy, Jr., 4952 Maryland Ave., St. Louis, Mo. Second Thursday, October, December, February, and April.

San Francisco Gynecological Society. *President,* T. Henshaw Kelly. *Secretary,* R. Glenn Craig, 490 Post Street, San Francisco, Calif. Regular meetings held second Friday in month, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.

Texas Association of Obstetricians and Gynecologists. *President,* Roy Grogan. *Secretary,* J. McIver, 714 Medical Arts Building, Dallas, Texas.

Michigan Society of Obstetricians and Gynecologists (formerly the Detroit Obstetrical and Gynecological Society). *President,* Norman F. Miller. *Secretary,* Harold C. Mack, 955 Fischer Bldg., Detroit, Mich. Meeting first Tuesday of each month from October to May (inclusive).

Obstetric Society of Syracuse Hospitals. *President,* Edward C. Hughes. *Secretary,* Nathan N. Cohen, 713 East Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.

Alabama Association of Obstetricians and Gynecologists. *President,* T. M. Boulware, Birmingham, Ala. *Secretary,* Eva F. Dodge, Montgomery, Ala.

San Antonio Obstetric Society. *President,* I. T. Cutter. *Secretary,* S. Foster Moore, Jr., San Antonio, Texas. Meetings held first Tuesday of each month at Gunter Hotel.

Seattle Gynecological Society. *President,* Glen N. Rotten. *Secretary,* R. Philip Smith, 1305 Fourth Avenue. Meetings third Wednesday.

Denver Obstetrical and Gynecological Society. *Secretary,* Emmett A. Mechler, 1612 Tremont St., Denver, Colo.

Wisconsin Society of Obstetrics and Gynecology. *President,* Roland S. Cron. *Secretary,* Robert E. McDonald, 425 E. Wisconsin Ave., Milwaukee, Wis. Meetings held in May and October.

San Diego Gynecological Society. *President,* Ralph Hoffman. *Secretary,* Purvis L. Martin, 2001 Fourth Ave., San Diego, Cal. Meetings held on the last Wednesday of each month.

North Dakota Society of Obstetrics and Gynecology. *President,* J. H. Fjelda. *Secretary,* Ralph E. Leigh, 111 North Fifth St., Grand Forks, N. D.